

GAZE, POSTURE, BALANCE, AND TRAINING EFFECTS IN PERSONS WITH  
MULTIPLE SCLEROSIS

by

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## ABSTRACT

Multiple Sclerosis (MS) is a chronic, neurological disorder characterized by imbalance and falls. Accurate perception and integration of three sensory inputs – the vestibular, vision, and somatosensory, is critical to produce human gaze and posture orientation. In MS, demyelination of pathways within the brainstem and cerebellum adversely affect gaze and postural stability. However, the deficits and the psychometric properties of these measures remain less examined. Moreover, the benefits of training on gaze and postural stability are unknown in MS.

This study examined the deficits in gaze stability, dynamic balance, and self-report measures in persons with MS as compared to controls; assessed the test-retest reliability and response stability of gaze stability, postural sway, and dynamic balance tests; and investigated the effects of training on gaze stability, galvanic-induced postural sway, dynamic balance, and self-report measures in persons with MS. We hypothesized that persons with MS will demonstrate deficits in gaze and postural stability; that study measures will demonstrate moderate to good reliability and acceptable response stability; and that persons with MS will demonstrate significant improvements after training.

Nineteen persons with MS at fall-risk and 14 controls were recruited and the assessments were carried out on 2 occasions. The participants then completed a 2-week training followed by re-assessments.

Persons with MS demonstrated significant differences in the gaze stability,

dynamic balance, and self-report measures versus controls. In addition, significant inter-relationships were found.

The majority of gaze stabilization measures demonstrated moderate while the postural sway and dynamic balance measures showed good reliability. The aVOR gain, FGA, and FSST showed SEM % <20 and MDD95% <20, suggesting acceptable response stability.

After training, gaze stability was achieved by recruiting substitutive oculomotor strategies whereas postural stability was achieved by sway response adaptations. Consistent improvements in dynamic balance and self-report measures suggest clinically meaningful changes.

Taken together, these findings support the study hypothesis and suggest that significant deficits in gaze and posture may be present in persons with MS. This highlights the utility of these assessments in fall-risk evaluations in persons with MS. Moreover, the different strategical mechanisms for improvements after training suggest the clinical value of a focused training intervention.

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## LIST OF ABBREVIATIONS

ABC	Activities-specific Balance Confidence
ADLs	Activities of Daily Living
AP	Antero-Posterior
AUC	Area Under the Curve
aVOR	angular Vestibulo-Ocular Reflex
BBT	Berg Balance Test
COP	Center of Pressure
CS	Compensatory Saccades
CV	Coefficient of Variation
DHI	Dizziness Handicap Inventory
EDSS	Expanded Disability Severity Scale
FGA	Functional Gait Assessment
FSST	Four Square Step Test
GPE	Gaze Position Error
GPS	Gaze and Postural Stabilization
GVS	Galvanic Vestibular Stimulation
HC	Healthy Controls
ICC	Intraclass Correlation Coefficient
ICF	International Classification of Function, Disability, and Health

MDD	Minimal Detectable Difference
ML	Medio-Lateral
MYHA	Maximal Yaw Head Acceleration
PwMS	Persons with Multiple Sclerosis
SEM	Standard Error of Measurement
vHIT	video Head Impulse Test
VOR	Vestibulo-Ocular Reflex
VSR	Vestibulo-Spinal Reflex

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## CHAPTER 1

### INTRODUCTION

Multiple Sclerosis (MS) is a chronic, demyelinating neurological disorder characterized by varying motor deficits such as spasticity, weakness, imbalance, and loss of functional mobility.<sup>1-3</sup> Balance dysfunction forms a major disabling symptom in Persons with MS (PwMS),<sup>4</sup> consequently leading to falls,<sup>5</sup> associated morbidities, considerable financial costs and mortality. A high rate of fall recurrence has been identified in PwMS.<sup>6</sup> Despite the high incidence, little is known about the different contributing factors to imbalance and falls in MS. Brainstem and cerebellar lesions have recently been linked to imbalance in PwMS, indicating that deficiencies in these regions may be central underlying factors.<sup>7,8</sup> Since falls significantly impact the activities and participation of PwMS, associations between brainstem and cerebellar dysfunction and imbalance need to be further investigated.

The brainstem and cerebellum are key central nervous system areas for reflexive sensorimotor control of eye-head coordination and postural balance,<sup>9,10</sup> which is a major function of the vestibular system. The vestibular system, in conjunction with the visual and somatosensory systems, provides afferent information that directly governs the static and dynamic orientation of human gaze and posture. To do this, the peripheral vestibular apparatus relays information on head angular velocity and linear acceleration to the

central vestibular structures, mainly comprised of the vestibular nuclei (brainstem) and cerebellum. The central structures process and pool these signals with other sensory information to estimate spatial head and body orientation (Figure 1.1). Accurate perception and integration of the three sensory inputs is, therefore, critical during daily activities. A deficit either in perception or integration of the vestibular sensations may result in impaired gaze, head and body orientation, and therefore, imbalance and falls in PwMS.<sup>9</sup> The vestibular system controls human gaze and posture by serving two important reflexes-vestibulo-ocular and vestibulo-spinal reflexes (Figure 1.2). To ensure clear vision during daily dynamic activities that require quick head movements such as driving, scanning shelves during grocery shopping, and running, the stabilization of images on fovea is important. The angular Vestibulo-Ocular Reflex (aVOR) generates an equal and opposite eye movement in response to rotational head motion which maintains the visual stability of a target and avoids blurriness (Figure 1.2 (a) and (b)).<sup>9</sup> When the aVOR is deficient, central compensatory eye movements such as vestibular-catch up saccades are produced (Figure 1.3).<sup>11, 12</sup> Thus, both the aVOR and saccades are vital mechanisms to achieve optimal gaze stability.<sup>13</sup> The Vestibulo-Spinal Reflex (VSR), on the other hand, is an assemblage of postural reflexes that activate the neck, trunk, and limb muscles to allow stabilization of the human body through space.<sup>9</sup> The postural stabilization mechanisms of the vestibular system are complex and less-known. Postural stability is achieved by combining the gravioceptive information from the vestibular peripheries with other inputs to create an internal map of the body's limits of stability (Figure 1.1 and 1.2 (a)). These limits in turn control the body's center of mass to maintain equilibrium within a static posture (such as quiet standing), as well as during postural

recovery after a destabilizing stimulus (such as a head tilt to one side). Therefore, the motor output from vestibular pathways is essential in maintaining the postural stability during static and dynamic activities of daily living.

Pathologies within these reflex pathways have been associated with gaze and postural difficulties.<sup>14, 15</sup> In MS, demyelination of the afferent or efferent vestibular nuclei complex pathways within the brainstem and cerebellum are proposed to adversely affect the gaze and postural stability due to either deficient output to the oculomotor or spinal motor neurons or poor regulation of these reflexes by the cerebellum (Figure 1.1 and 1.2). However, impairments in the vestibular-related gaze and postural stability function still remain less examined in PwMS.

The gaze stabilization function can be examined in several ways. Due to the orientation of semicircular canal afferent apparatus in the inner ear, head rotations can be detected in three-dimensional axes. However, the majority of current clinical testing is still focused on the horizontal canal aVOR function due to the ease of testing.<sup>16</sup> Thus, the neuroanatomy of horizontal aVOR deserves particular attention amongst the battery of vestibular ocular examinations in individuals with vestibular complaints. Horizontal aVOR function can be evaluated by clinical measures such as bedside head thrust tests, dynamic visual acuity tests; and by laboratory-based measures such as canal irrigation, rotatory chair test, instrumented visual acuity tests, etc. (Table 1.1).<sup>9, 16, 17</sup> Additional measures such as ocular vestibular-evoked potentials and verticality are known tests for different vestibular structures (Table 1.1).<sup>9, 16, 17</sup> A new clinical measure of dynamic semicircular canal function has been recently made available, the videographic Head Impulse Test (vHIT), which records head and eye movement during and immediately



after passive head rotations and is based on the bedside head thrust test.<sup>18</sup> The validity of vHIT has been established in people with peripheral vestibular disorders.<sup>19, 20</sup> Although a few studies have reported altered vestibular function, owing to peripheral and central pathologies, in PwMS,<sup>21, 22</sup> the horizontal aVOR function has not been explored utilizing the vHIT system yet.

Impairments in postural stability have frequently been assessed by posturography, vestibular-evoked myogenic potentials and dynamic balance measures in PwMS (Table 1.1).<sup>16, 21, 22</sup> Posturography measures the body's center of mass position and movement during a standing postural sway test<sup>23</sup> or during a destabilizing vestibular-evoked postural task. Vestibular stimuli can be provided using Galvanic Vestibular Stimulation (GVS), where a direct low-amplitude electrical impulse stimulates the eighth cranial nerve, resulting in a compensatory sway response by the head and body opposite to the perceived movement.<sup>24, 25</sup> Although the galvanic postural sway test has been used reliably in normal individuals,<sup>25</sup> its utility in assessing the postural stability and in determining the effect of balance interventions in PwMS remains less known. Clinical measures of dynamic balance are also often utilized to determine postural instability in people with vestibular disorders.<sup>26</sup> These performance-based measures include, but are not restricted to, multidirectional reaching, gait indices, timed walking, and stair climbing tests. Diminished scores on these clinical balance measures have been found in PwMS,<sup>27</sup> but the specific neural correlates for impaired gaze and posture in a central vestibular dysfunction such as MS has not been established yet. Moreover, the psychometric properties of the above-discussed measures of gaze and postural stability have not been determined in PwMS.

Vestibular rehabilitation encompasses exercises addressing adaptation, substitution, habituation, gait, posture, strengthening, flexibility, and endurance to maximize the gaze and postural stability as well as functioning in people with different vestibular disorders.<sup>9</sup> Of these, Gaze and Postural Stabilization (GPS) exercises have shown improvements in vertigo and balance in persons with vestibular complaints,<sup>28, 29</sup> suggesting that the nervous system fosters the ability to recover from the disarrayed afferent vestibular input and impaired central sensory integration. The increasingly recognized fall-risk in PwMS has spurred various fall-rehabilitation interventions, but very few studies have verified the benefit of vestibular rehabilitation in PwMS.<sup>30, 31</sup> To date, no study has attempted to examine the neural correlates of GPS training to improve gaze and postural stability in PwMS. As a result, the current clinical interventions to improve balance dysfunction in PwMS are generic and nonspecific.

Due to the identified gaps in knowledge on impairments in gaze and postural stability mechanisms as well as the effects of a targeted GPS intervention in PwMS, this study attempted to highlight the vestibular deficits and adaptation by utilizing specific outcome measures in this population. In general, the goal of this dissertation project was threefold: first, to identify deficits in the gaze stability, dynamic balance, and participation measures in persons with MS at fall-risk as compared to healthy controls; second, to assess the test-retest reliability and response stability of gaze stability, postural sway, and dynamic balance tests in persons with MS at fall-risk and controls; third, to determine the effects of home-based GPS training on gaze stability, galvanic-induced postural sway, dynamic balance, and participation in persons with MS at fall-risk. The overall purpose of this study was to provide information on vestibular contributions to

balance deficits and to determine the efficacy of adaptation exercises on gaze and postural instability in PwMS. The global hypothesis of this study was that PwMS at fall-risk will demonstrate deficits in gaze and postural stability mechanisms relative to controls and that they will also demonstrate significant improvements in gaze and postural stability mechanisms after a GPS intervention. To meet this purpose, the following aims were devised:

*Specific Aim 1: To determine the extent and characteristics of deficits in gaze, postural stability, and participation in PwMS at fall-risk as compared to neurologically healthy controls.*

*Specific Aim 2: To examine the test-retest reliability and response stability of gaze, and postural stabilization tests in MS as well as neurologically healthy controls.*

*Specific Aim 3: To examine the extent of adaptation in gaze, postural stability, and participation in PwMS at fall-risk via controlled exposure to error signals that typically induce motor learning (i.e., retinal slip and postural perturbation).*

To achieve our overall purpose and test our hypothesis and specific aims, a series of investigations were carried out. These studies and their rationale are briefly described below and their detailed description is provided in the chapters that follow.

### Gaze, dynamic balance, and participation deficits in PwMS

Impaired gaze stability, nystagmus, dizziness, and locomotor dysfunction are frequent findings in PwMS.<sup>1, 7, 32</sup> Impaired postural control<sup>21, 33</sup> and deficient central sensory integration<sup>33</sup> has been previously demonstrated in PwMS. Despite these findings, there has been little focus on gaze stability during head rotations at high movement

velocities and its quantification in PwMS. Additionally, information on dynamic balance measures such as the Functional Gait Assessment (FGA) and Four Square Step Test (FSST) and self-report participation measures such as the Dizziness Handicap Inventory (DHI) and Activities-specific Balance Confidence (ABC) is lacking in PwMS at identified fall-risk.

Our first investigation aimed to 1) compare the gaze stability in response to high-velocity horizontal head rotations in PwMS at fall-risk to neurologically healthy controls, 2) compare the dynamic balance task performance and self-reported participation in PwMS at fall-risk to controls, and 3) examine the relationship between gaze stability performance, dynamic balance task performance, and self-reported participation in the overall sample. We hypothesized that measures of gaze stability, dynamic balance, and self-report participation would be altered in PwMS at fall-risk as compared with age-matched controls. We also hypothesized that significant and clinically meaningful correlations would be demonstrated between gaze stability, dynamic balance, and self-report participation measures.

#### Test-retest reliability and response stability of gaze stability, postural sway, and dynamic balance tests in PwMS and controls

Although the validity of gaze stability (as measured by vHIT) has been established in people with vestibular disorders,<sup>18-20</sup> information on its reliability in PwMS remains unknown. Similarly, poor performance on postural sway and dynamic balance tasks have been linked to fall-risk and balance deficits,<sup>34,35</sup> but the psychometric properties of these tests remain unclear in PwMS.

Our second study intended to examine the 1) test-retest reliability and 2) response stability of gaze stabilization, standing postural sway, and dynamic balance assessments in PwMS as well as age-matched healthy controls across repeated sessions. We hypothesized that these measures would demonstrate moderate to good reliability and acceptable response stability in PwMS and controls.

The effect of GPS training on gaze, galvanic-induced postural sway,  
dynamic balance, and participation in PwMS

Previous research has examined the efficacy of vestibular rehabilitation on clinical measures of balance, postural control, and dizziness in PwMS,<sup>30, 31, 36</sup> but the effect of GPS exercises on physiologic measures of vestibular function (such as the gaze and vestibular-evoked postural stability function) remain unidentified. Moreover, since current balance interventions in PwMS frequently utilize eye and head movement exercises, a need to examine the effect of GPS intervention on vestibular physiology exists.

The third study, therefore, aimed to determine the effects of a 2-week, self-administered GPS training intervention on gaze stability, galvanic-induced postural sway, dynamic balance, and self-reported participation in PwMS at fall-risk. We hypothesized that PwMS will demonstrate significant improvements in gaze stability, galvanic vestibular stimulation-induced postural sway, dynamic balance, and self-reported participation posttraining.

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Table 1.1. Tests of vestibular function in PwMS

Tests	Function assessed	Disadvantage	Results in MS
<b><i>Gaze stability tests</i></b>			
Bedside head thrust	SCC pathways	requires experience, misses covert-saccades	Normal <sup>21, 37</sup>
Dynamic visual acuity	SCC pathways	requires experience, not-specific towards the side of lesion	Not known
Caloric irrigation	SCC pathways	low-acceleration, cumbersome	Abnormal <sup>21</sup>
Rotary chair	SCC pathways	cumbersome	Abnormal <sup>21, 14</sup>
Head thrust with Scleral search coils	SCC pathways	laboratory-based, not suitable for routine clinical use	Not known
Ocular VEMPs	otolith pathways	laboratory-based, not suitable for aVOR testing	Abnormal latencies <sup>22, 38</sup>
Subjective visual vertical	otolith pathways	not suitable for aVOR testing	Abnormal <sup>32</sup>
Head thrust with videographic system	SCC pathways	not known	Not known
<b><i>Postural stability tests</i></b>			
Clinical balance (mini-Best and Berg)	unspecific	lack of specificity towards vestibular function, not-specific towards the side of lesion	Abnormal <sup>39</sup>
Posturography	unspecific	lack of specificity towards vestibular function, not-specific towards the side of lesion	Abnormal <sup>21, 40, 41, 42</sup>
Cervical VEMPs	otolith pathways	laboratory-based, not suitable for routine clinical use	Abnormal latencies, <sup>38, 43, 44</sup> abnormal amplitudes <sup>43, 44</sup>
Galvanic-induced postural sway test	SCC pathways	laboratory-based	Not known

Abbreviations. SCC, Semi Circular Canal; VEMPS, Vestibular Evoked Myogenic Potentials

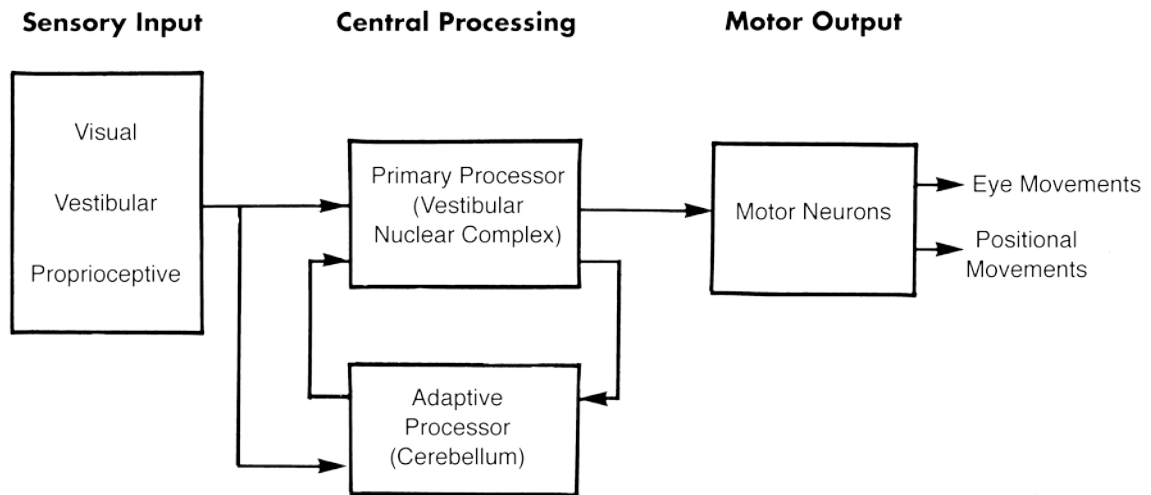
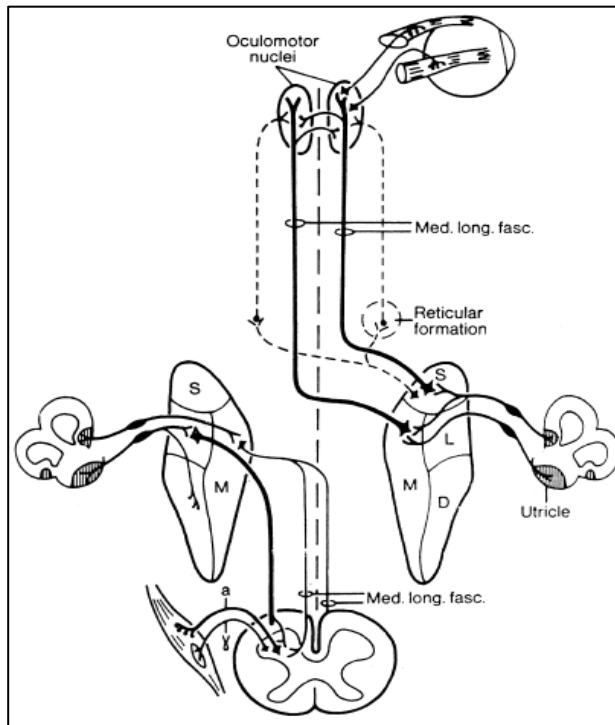


Figure 1.1. The human vestibular system (adapted from Herdman 2007).<sup>9</sup>



(a)



(b)

Figure 1.2. Sensorimotor gaze and postural reflexes.

(a) The angular Vestibulo-Ocular Reflex (aVOR) and Vestibulo-Spinal Reflex (VSR) arcs. (adapted from Herdman 2007).<sup>9</sup>

(b) The horizontal aVOR in a normal healthy subject depicting the reflexive equal and opposite eye motion to head rotation in the horizontal plane.

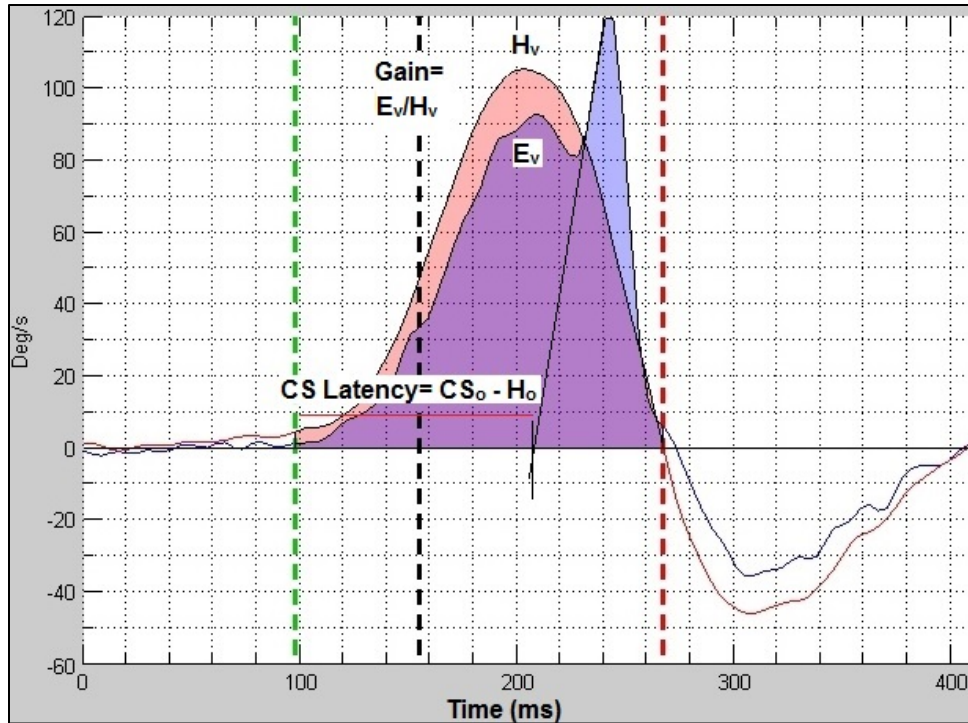


Figure 1.3. The gaze stability function: The figure demonstrates a deficient vestibular-driven aVOR in response to the head rotation, supplemented by a centrally-driven compensatory catch-up saccade to maintain the stabilization of gaze at a target. The eye velocity has been inverted for ease of comparison.

Abbreviations.  $H_v$ , Head velocity;  $E_v$ , Eye velocity; Gain, aVOR gain ( $E_v/H_v$ );  $H_o$ , Head onset; CS, Compensatory Saccade;  $CS_o$ , CS onset. Green dotted line represents the onset of head movement. Black dotted line represents the maximal yaw head acceleration. Red dotted line represents the return of the head movement velocity to zero.

## CHAPTER 2

### GAZE STABILITY, DYNAMIC BALANCE, AND PARTICIPATION DEFICITS IN PEOPLE WITH MULTIPLE SCLEROSIS AT FALL-RISK

#### Abstract

Despite dizziness being common, few studies have examined gaze stability in Persons with Multiple Sclerosis (PwMS). We aimed to 1) determine differences in gaze stability, dynamic balance, and participation measures between PwMS and controls, and 2) examine relationships between gaze stability, dynamic balance, and participation. Nineteen ambulatory PwMS at fall-risk and 14 age-matched controls were recruited. Outcomes included (a) gaze stability [angular Vestibulo-Ocular Reflex (aVOR) gain (ratio of eye to head velocity); number of Compensatory Saccades (CS) per head rotation; CS latency; gaze position error; Coefficient of Variation (CV) of aVOR gain], (b) dynamic balance [Functional Gait Assessment, FGA; four square step test], (c) participation [dizziness handicap inventory; activities-specific balance confidence scale]. Separate independent t-tests and Pearson's correlations were calculated. PwMS were age =  $53 \pm 11.7$  yrs, falls/yr =  $4.2 \pm 3.3$ , Berg Balance test score =  $46 \pm 7.1$  (all mean  $\pm$  SD). PwMS demonstrated significant ( $p < 0.05$ ) impairments in gaze stability, dynamic balance, and participation measures compared to controls. CV of aVOR gain and CS latency were

significantly correlated with FGA. Deficits and correlations across a spectrum of disability measures highlight the relevance of gaze and postural stability assessment in PwMS.

### Introduction

Falls and imbalance are major disabling symptoms in Persons with Multiple Sclerosis (PwMS).<sup>1</sup> A high incidence of falls has been reported in PwMS (50-60%)<sup>2,3</sup> which forms an important health concern due to its associations with injury-related morbidities, mortality, and financial costs. Despite the high prevalence of falls, factors contributing to balance dysfunction have not been well-studied in PwMS. Brainstem and cerebellum afflictions have recently been associated with imbalance in PwMS highlighting the need for further investigation.<sup>4,5</sup>

Accurate perception and integration of vestibular sensations is required to maintain dynamic gaze and postural stability. A deficit in either may lead to imbalance and falls.<sup>6</sup> These instabilities may be the result of pathology within the vestibulo-ocular and vestibulo-spinal pathways of the brainstem and cerebellum.<sup>6</sup> The demyelination of afferent or efferent pathways to and from the vestibular nuclei may adversely affect the angular Vestibulo-Ocular Reflex (aVOR) and vestibulo-spinal function in PwMS. PwMS who exhibit abnormal eye movements present with greater disability and impaired cerebellar and/or brainstem scores in part due to lesions in the medial longitudinal fasciculus.<sup>7,8</sup> Impaired aVOR, vestibular evoked potentials, nystagmus, dizziness, posturography, and locomotor dysfunction have been reported in PwMS.<sup>9-13</sup> Despite these findings, there has been little quantification of gaze stability during rapid head

rotations in PwMS.

In order to provide insight into potential deficits in vestibulo-ocular function in PwMS, our primary objective was to compare gaze stability in response to high-velocity horizontal head rotations in PwMS at fall-risk with age-matched controls. We hypothesized that measures of gaze stability would be altered in PwMS as compared to controls. Secondary objectives of the study were to 1) compare dynamic balance performance and participation measures in PwMS and age-matched controls and 2) examine the relationship between gaze stability, dynamic balance, and participation measures in the overall sample. We hypothesized that measures of dynamic balance and participation would be altered in PwMS at fall-risk as compared with controls as well as that significant and clinically meaningful correlations would be demonstrated between gaze stability, dynamic balance, and participation measures.

## Methods

### Participants

Thirty-nine PwMS from neurology clinics and the local chapter of the National MS Society in Salt Lake City, Utah were screened (Figure 2.1). Neurologically Healthy Controls (HC), matched for age, were recruited from the local community. Based on previously observed effect sizes for aVOR gain using video Head Impulse Testing (vHIT),<sup>14</sup> we anticipated two groups of 15 would adequately power this study. Inclusion criteria for PwMS included: confirmed MS diagnosis; Expanded Disability Status Scale (EDSS) score of  $\leq 6.5$ ; able to stand 30 seconds without support; fall-risk determined by Activities-specific Balance Confidence (ABC) score  $<70$ ,  $\geq 2$  retrospective falls per year,



Berg balance test score <44, or Dizziness Handicap Inventory (DHI) > 59.<sup>2</sup> Exclusion criteria for PwMS were: history of other central and peripheral nervous system injury or neuro-otologic condition besides MS, internuclear ophthalmoparesis or ophthalmoplegia, and history of MS relapse in the previous 3 months. Additionally, PwMS and controls were excluded if they had orthopedic, medical, surgical, or cognitive limitations that would limit their study participation.

### Study procedures

After obtaining institutional review board approved informed consent, a general medical history, MS-specific history, and fall-history were gathered via personal interview. Thereafter, fall-risk status was determined. In all PwMS at fall-risk, in order to exclude individuals with peripheral vestibular pathologies, a clinical vestibular examination was performed which was comprised of oculomotor range of motion, saccades, bedside HIT, VOR cancellation, and test of skew.<sup>6</sup> We also examined for spontaneous, head shake, and positional nystagmus using an infrared video goggles system. Individuals who met the inclusion criteria underwent a neurological examination (EDSS).<sup>15</sup> Thereafter, the gaze stability and dynamic balance tests were completed on a separate assessment day (Figure 2.1).

### Measures

In order to determine the breadth of differences between PwMS and controls, our outcomes encompassed the 3 domains of the World Health Organization's International Classification of Function, Disability, and Health (ICF) model.<sup>16</sup>

*The body structure and function domain was quantified by gaze stability measures.* Gaze stability was determined using vHIT goggles (GN Otometrics, Denmark), which have been recently validated in people with VOR deficits (Figure 2.2 (a) and (b)).<sup>17</sup> Subjects were seated and instructed to fixate their eyes at a target on the wall 1m away in dim light. A single examiner administered passive horizontal (yaw) head impulses (amplitude 10°–20°) to each side with the goal of collecting at least eight trials suitable for data analyses. Peak head velocity of the impulses ranged from 120° to 350°/second. The right eye velocity was measured using a small, lightweight, high-speed digital video camera with 250Hz sampling rate, mounted on a lightweight frame. An elastic strap minimized slippage of the camera relative to the head. The image of the eye was reflected from a mirror to the camera. Changes in head velocity (the stimulus) were measured by a rate sensor. The camera, mirror, and rate sensor were rigidly integrated into a spectacle frame. The manufacturer's proprietary software captured and stored the head and eye velocity data (the response).

The dependent variables of gaze stability (Figure 2.3(a) and (b)) included aVOR gain, number of Compensatory Saccades per Head Rotation (CS/HR), CS latency, Gaze Position Error (GPE), and variability (Coefficient of Variation, CV) of aVOR gain. The aVOR gain was calculated as the ratio of the de-saccaded eye velocity Area Under the Curve (AUC) over the head velocity AUC between the onset of the head impulse to the moment when head velocity returned to zero.<sup>14</sup> The onset of head movement was determined in one of two ways. Preferentially, based on the methods of MacDougall et al.<sup>14</sup> the time point of 60 msec prior to Maximal Yaw Head Acceleration (MYHA) was identified as the head onset. The accuracy of this method was confirmed by visual

analysis of head velocity traces. In those few instances where the 60 msec rule appeared to inaccurately identify the head onset upon visual inspection, the last time point when the head velocity crossed zero and continually moved in the intended direction was identified as the head onset. Although we tested gaze stability during head rotations to left and right directions, we expected that PwMS would produce varied and asymmetrical deficits; therefore, we utilized the performance of the worst functioning side as the operational definition for aVOR gain. The CS/HR were manually counted. The CS was defined as a horizontal eye rotation occurring during the head rotation to assist a deficient aVOR; thus, it occurred in the direction of the vestibular slow component.<sup>18</sup> The CS characteristically exhibited a visible step in the horizontal eye position plot and was identified as overt (occurrence of CS within 170 milliseconds *after* head velocity reached zero<sup>19</sup> and yaw acceleration  $\geq 5,000 \text{ deg/s}^2$ ) or covert (occurrence of CS *during* the head rotation and yaw acceleration either  $\geq$  or  $< 5,000 \text{ deg/s}^2$ ). The CS latency was determined as the duration of time between onset of head acceleration to onset of first identifiable CS. The GPE was defined as the target position minus eye position at the end of the head impulse. The CV of aVOR gain was calculated as the ratio of the aVOR Standard Deviation (SD) to the aVOR mean to determine within-subject variation.

***The activity domain was assessed by dynamic balance measures.*** The dependent variables were the Functional Gait Assessment (FGA) and the Four Square Step Test (FSST). The FGA is a 10-item test that assesses stability during walking on a marked 6-m (20-ft) length and 12-inch wide walkway. Participants performed each of the 10 items once and were scored from 0 (severe impairment) to 3 (normal) on each item. The reliability and validity of the FGA has been established.<sup>20</sup> The FSST assesses an

individual's ability to change directions while stepping. A square is formed with four canes resting flat on the floor and the subject is asked to step as fast as possible in each square.<sup>21</sup> The procedure was demonstrated and one practice trial was allowed. The fastest time of 1 trial from 2 completed trials was recorded in seconds. The reliability and criterion validity of FSST has been established.<sup>21-23</sup>

***The participation domain was measured by 2 self-report instruments.*** The dependent variables were: (a) DHI, which is a 25-item self-assessment inventory to evaluate the self-perceived handicap imposed by dizziness or unsteadiness. The scale contains 3 domains: functional, physical, and emotional. The total summed score ranges from 0 to 100 and was utilized, with higher scores indicating greater handicap. The reliability and validity of DHI has been established,<sup>2,24</sup> (b) ABC, which is a 16-item self-reported measure of balance confidence in performing daily activities. Each question requires an individual to grade himself on a scale of 0 to 100 percent for their level of confidence<sup>25</sup> and higher scores indicate greater confidence. The average score for 16 items was analyzed. The ABC has been shown to be reliable and valid<sup>2,24</sup> and to accurately predict falls in PwMS.<sup>26</sup>

#### Data reduction and analysis

The collected raw data from the vHIT was exported to custom software written in Matlab (Math-Works, Natick MA) for screening and analysis. Standardized screening measures were employed to discard trials with blinks and movement artifacts.<sup>27</sup> Briefly, trials were screened for inclusion using the following criteria: visual inspection for appropriateness and smoothness of eye and head movement; blink identification by either

detecting a biphasic deflection in lateral eye movement velocity trace, or an acute deflection in pitch eye movement velocity trace.<sup>27</sup>

Between-group differences in PwMS and HC were determined by separate independent t-tests for each of the dependent variables. Measures of between-group effect sizes were calculated for each of the nine dependent variables using Cohen's d. Given the pilot nature of this study, no correction was applied for the multiple t-tests, which were interpreted using an  $\alpha$  level of 0.05. Correlations between gaze stability, dynamic balance, and participation were tested using the Pearson's correlation coefficient. SPSS version 20.0 (IBM Corporation, Armonk, NY) was used for all analyses.

### Results

The MS Group was comprised of 3M/16F with a mean  $\pm$  SD age =  $53 \pm 11.7$  yrs and falls/yr =  $4.2 \pm 3.3$ , while the HC Group included 5M/9F with age =  $55 \pm 11.9$  yrs and falls/yr =  $0.07 \pm 0.3$  (Table 1.1).

Both groups demonstrated the presence of CS/HR, mean  $\pm$  SD in PwMS =  $0.61 \pm 0.34$ , and HC =  $0.42 \pm 0.22$  (Table 2.2). In contrast with the HC, PwMS demonstrated significant ( $p < 0.05$ ) deficiencies in mean CS/HR, CS latency, CV of aVOR gain, and impairments in FGA, FSST, ABC and DHI; however, no differences were found in mean aVOR gain and GPE (Figure 2.4 (a), (b), and (c); Table 2.2).

Significant correlations were found between CS latency and FGA ( $r = 0.38$ ) and CV of aVOR gain and FGA ( $r = -0.51$ ; Table 2.3).

## Discussion

Gaze and postural stability mechanisms are essential in maintenance of balance and prevention of falls. To our knowledge, deficits in gaze stability function in PwMS and their relationship with measures of activity limitation and participation have not been previously examined. This study demonstrated significant differences in gaze stability (CS/HR, CS latency, CV of aVOR gain), dynamic balance (FGA, FSST), and participation (DHI and ABC) in PwMS as compared to neurologically healthy controls. In addition, significant relationships between CS latency, CV of aVOR gain, and FGA were found. Contrary to the hypotheses, no differences in aVOR gain and GPE were seen between groups.

### Body structure and function: The nature of gaze stabilization deficits in PwMS

Relative to controls, PwMS recruited a greater number of CS at a shorter latency and demonstrated more variability (CV) of aVOR gain. These findings suggest deficiencies within the vestibular-driven eye response to passive horizontal head rotation, and that saccades were recruited as a corrective mechanism to improve gaze stabilization of the target [Figure 2.3(b)]. Previous studies have shown that CS are an effective compensatory mechanism for decreased aVOR gain in people with peripheral vestibulopathies and have linked them to reduced gaze position error.<sup>19, 28</sup> Although these findings imply a decreased aVOR gain, we did not find any differences in mean gain in our sample. However, greater variability (CV) of aVOR gain was observed in PwMS as compared to HC ( $p=0.05$ ). This variability can best be understood as an increase in the

within-subject inconsistency of individual aVOR responses to head rotations.

Functionally, we would expect that such inconsistencies in gaze stabilization might manifest itself as complaints of dizziness, motion sensitivity, and decreased balance confidence during daily activities and community mobility. The presence of DHI and ABC impairments relative to controls supports this line of reasoning.

These observations suggest impairments in the horizontal VOR neuroanatomic pathways in PwMS. Our results are consistent with previous studies that have demonstrated varying vestibular ocular abnormalities ranging from the presence of CS in a bedside HIT, altered vertical perception, nystagmus, as well as prolonged latencies and decreased amplitudes on vestibular evoked potentials.<sup>7-9, 12, 13</sup> Taken together, deficiencies in semicircular canal and otolithic pathways, as well as oculomotor function, indicate that brainstem and cerebellar vestibular pathways may be affected in PwMS. Although imaging of these nuclei and pathways was beyond the scope of this study, the synthesis of these results with previous work strongly suggests that brainstem imaging may provide insight into the neural substrates of the observed vestibular deficits.

#### Activity and participation: The nature of dynamic balance and participation deficits in PwMS

Deficits in both measures of activity (FGA and FSST) were found in PwMS as opposed to controls. These findings are clinically important because these measures can identify fall-risk and balance deficits in people with vestibular disorders.<sup>22, 29</sup> Although the DGI has been previously studied in PwMS,<sup>2, 26</sup> less is known about the FGA. Similarly, few studies have examined the FSST performance in PwMS.<sup>3, 23</sup> The impaired

performance on dynamic balance tests noted in this study highlights the importance of including measures of dynamic balance in assessment and management of PwMS at fall-risk. Our results provide support to the recent recommendations from the International MS Falls Prevention Research Network for using these assessments.<sup>30</sup>

Persons with MS also demonstrated impaired participation scores compared to controls. The DHI scores seen in our sample (mean= 47.7) are indicative of the substantial impact that dizziness had on the functional, physical, and emotional well-being of PwMS. Similarly, decreased ABC scores highlight the lack of balance confidence in performing activities of daily living. These results are consistent with previous work in PwMS for DHI 2 and ABC.<sup>2, 26</sup> In general, these findings provide clinically useful detail to guide patient-oriented treatment goals and support the use of participation outcomes in MS trials as recommended.<sup>31</sup>

#### Relationship between the ICF domains

In the overall study sample (PwMS and HC), there was a fair-to-moderate relationship<sup>32</sup> between the CS latency and variability (CV) of aVOR gain with that of FGA, such that early onset CS latency and higher CV of aVOR gain was associated with decreased scores on FGA. While such a relationship does not indicate cause and effect, two potential explanations are worthy of further study. First, the vestibulo-ocular and vestibulo-spinal pathways may be concomitantly affected resulting in simultaneous deficits in gaze stability and dynamic balance in PwMS. Similar findings have been reported earlier where concurrent deficits and correlations between cortical proprioceptive tract integrity and balance control have been identified.<sup>33</sup> Another



possibility is that the compromised gaze stability produced impairments in dynamic balance. This may be possible as the FGA is comprised of several walking tasks incorporating the need for gaze stabilization via aVOR mechanisms (horizontal and vertical head turns, obstacle avoidance). Such demands on vestibular function may result in a lower overall score. Despite the observed correlations in our study, gaze stability only accounted for a moderate amount of variance in dynamic balance. Future research should expand the range of physiologic measures to include strength, fatigue, proprioception, coordination, and cognition that may account for additional variance in activity performance in MS.

Deficits in gaze stability did not directly relate to participation. These results are in agreement with previous work that demonstrated poor correlation between gaze stability measured by vHIT and self-reported dizziness handicap in individuals with vertigo, dizziness, or imbalance.<sup>34</sup> One reason for this finding can be the separate nature of constructs being measured. Another possible reason can be the lack of sensitivity of these self-report measures to capture difficulties in daily activities due to gaze instability. Further exploration and development of self-report measures to effectively evaluate the influence of gaze instability on daily activities is needed.<sup>35</sup>

Although this study demonstrated gaze stability and dynamic balance deficits in PwMS, these results should be interpreted with caution based on a relatively small sample size. Secondly, by design, the study limited gaze stability measurement to rapid, passive yaw rotation. Thus, no inferences can be made for deficits in lower velocity head movements or in the pitch planes of head motion. Lastly, the lack of structural or functional neuroimaging for determining the involvement of vestibulo-ocular and

vestibulo-spinal pathways in the brainstem and cerebellum limits our knowledge of the neural substrates for the observed deficits. Future research should investigate all canal planes via vHIT, include other measures of vestibular structures and function (such as dynamic visual acuity, vestibular evoked potentials, imaging), and examine the response to therapeutic interventions targeted at improving gaze and postural stability, improving dynamic balance performance, and reducing participation restrictions.

### Conclusion

Deficits in gaze stability, dynamic balance, and participation were identified in PwMS. These results suggest an increased risk of oscillopsia and falls. Poor gaze stability related to poor dynamic balance performance, emphasizing that gaze stability examinations should be included in balance assessments for PwMS at fall-risk.

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Table 2.1. Descriptive Statistics<sup>a</sup>

	MS (n=19)	HC (n=14)
Gender (M/F)	3/16	5/9
Age	53.4 ± 11.66 (47.80-59.04)	54.64 ± 11.88 (47.78-61.50)
EDSS (min-max)	4.95 ± 1.0 (3.5-6.5)	-
Diagnosis Duration (yrs)	16 ± 11.44 (10.49-21.51)	-
BBT	46.37 ± 7.10 (42.94-49.79)	55.4 ± 1.26 (54.49-56.31)
falls/yr	4.16 ± 3.35 (2.54-5.76)	0.07 ± 0.27 (-0.08-0.23)
Peak head velocity (degrees/sec)	187.53 ± 18.08 (178.81-196.24)	185.81 ± 19.02 (174.83-196.79)

<sup>a</sup>All values are mean (standard deviation)/95% confidence interval unless otherwise indicated.

Abbreviations. MS: Multiple Sclerosis.

Table 2.2. Independent Samples t-test.

	MS (n=19) Mean $\pm$ SD	HC (n=14) Mean $\pm$ SD	<i>p</i>	MD $\pm$ SED	95% CI	Effect size
<i>Body structure and function</i>						
aVOR gain	0.89 $\pm$ 0.08	0.90 $\pm$ 0.06	0.27	0.01 $\pm$ 0.03	-0.04, 0.07	0.14
CS/HR <sup>a</sup>	<b>0.61 <math>\pm</math> 0.34</b>	<b>0.42 <math>\pm</math> 0.22</b>	<b>0.03</b>	<b>-0.19 <math>\pm</math> 0.10</b>	<b>-0.39, 0.01</b>	<b>0.66</b>
CS latency (ms) <sup>a</sup>	<b>222.71 <math>\pm</math> 53.59</b>	<b>271.45 <math>\pm</math> 38.66</b>	<b>0.01</b>	<b>48.74 <math>\pm</math> 17.60</b>	<b>12.69, 84.79</b>	<b>1.05</b>
GPE	2.30 $\pm$ 1.14	2.19 $\pm$ 0.76	0.37	-0.12 $\pm$ 0.35	-0.83, 0.60	0.11
Gain CV <sup>b</sup>	<b>0.07 <math>\pm</math> 0.02</b>	<b>0.06 <math>\pm</math> 0.01</b>	<b>0.05</b>	<b>-0.01 <math>\pm</math> 0.01</b>	<b>-0.02, 0.00</b>	<b>0.62</b>
<i>Activity</i>						
FGA <sup>a</sup>	<b>15.0 <math>\pm</math> 4.61</b>	<b>27.07 <math>\pm</math> 2.30</b>	<b>&lt;0.001</b>	<b>12.07 <math>\pm</math> 1.22</b>	<b>9.57, 14.58</b>	<b>3.26</b>
FSST <sup>a</sup>	<b>13.20 <math>\pm</math> 7.08</b>	<b>7.05 <math>\pm</math> 1.79</b>	<b>&lt;0.001</b>	<b>-6.14 <math>\pm</math> 1.74</b>	<b>-9.77, -2.52</b>	<b>1.16</b>
<i>Participation</i>						
DHI <sup>a</sup>	<b>47.68 <math>\pm</math> 24.46</b>	<b>0.40 <math>\pm</math> 0.84</b>	<b>&lt;0.001</b>	<b>-47.28 <math>\pm</math> 5.62</b>	<b>-59.08, -35.48</b>	<b>2.45</b>
ABC <sup>a</sup>	<b>55.15 <math>\pm</math> 19.07</b>	<b>96.03 <math>\pm</math> 5.02</b>	<b>&lt;0.001</b>	<b>40.88 <math>\pm</math> 4.65</b>	<b>31.23, 50.53</b>	<b>2.67</b>

a  $p < 0.05$  one-tailed significance (bold)

b  $p = 0.05$  one-tailed significance (bold)

Abbreviations. MS: Multiple Sclerosis; SD: Standard Deviation; MD  $\pm$  SED: Mean Difference  $\pm$  Standard Error of Difference; CI: Confidence Interval of the difference; CS/HR: Compensatory Saccades per Head Rotation.



Table 2.3. Pearson Correlations between measured outcome variables

	CS/HR	CS latency	GPE	Gain CV	FGA	FSST	DHI	ABC
aVOR gain	<b>-.66<sup>a</sup></b>	<b>-.38<sup>a</sup></b>	<b>-.90<sup>a</sup></b>	<b>-.67<sup>a</sup></b>	0.26	0.15	0.05	0.07
CS/HR	1	<b>.50<sup>a</sup></b>	<b>.55<sup>a</sup></b>	<b>.42<sup>a</sup></b>	-.27	-.09	.08	-.17
CS latency (ms)		1	.24	-.15	<b>.38<sup>a</sup></b>	-.15	-.19	.26
GPE			1	<b>.67<sup>a</sup></b>	-.24	-.19	-.16	0.00
Gain CV				1	<b>-.51<sup>a</sup></b>	.16	.16	-.32
FGA					1	<b>-.70<sup>a</sup></b>	<b>-.71<sup>a</sup></b>	<b>.81<sup>a</sup></b>
FSST						1	<b>.61<sup>a</sup></b>	<b>-.54<sup>a</sup></b>
DHI							1	<b>-.88<sup>a</sup></b>
ABC								1

a. Correlation is significant at the 0.05 level (2-tailed) – in bold

Abbreviations. CS/HR: Compensatory Saccades per Head Rotation.

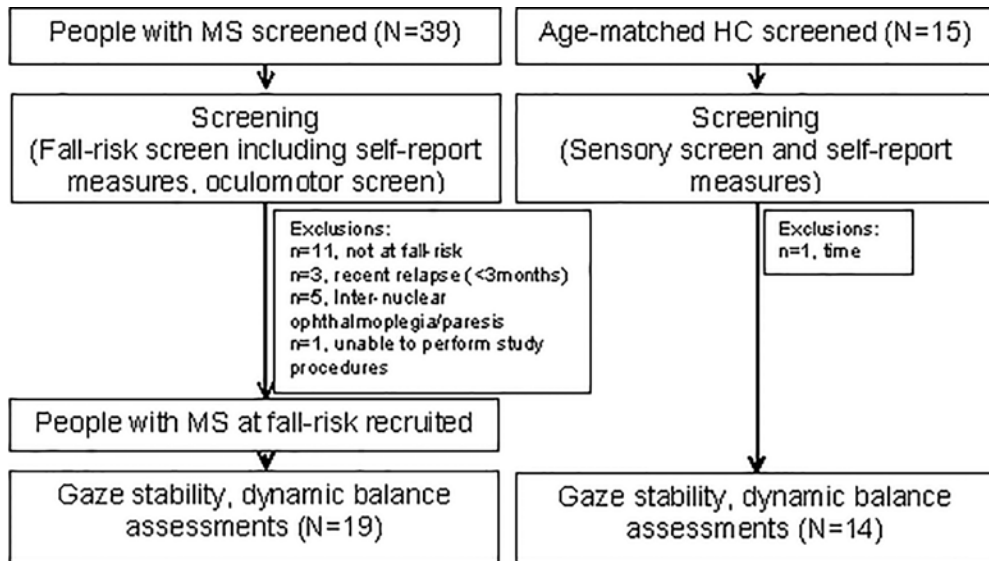


Figure 2.1: Diagram illustrating the flow of participants through the trial.

Abbreviations. MS: Multiple Sclerosis.



(a)

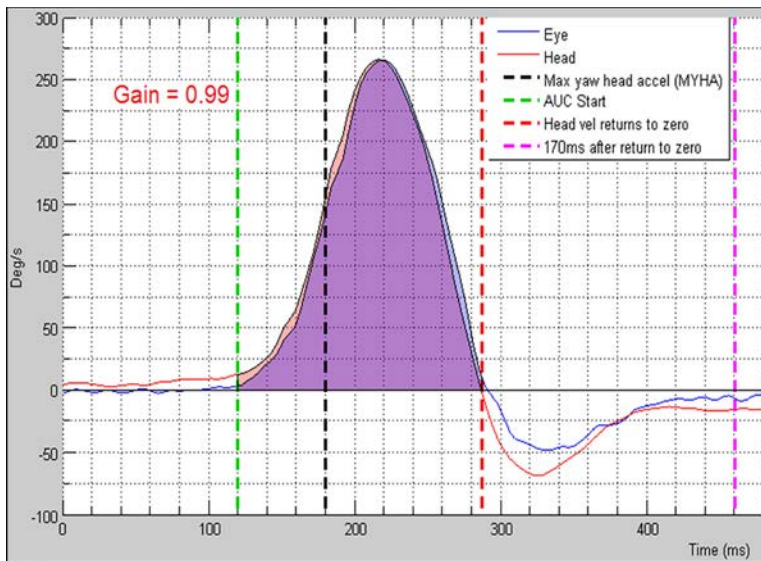


(b)

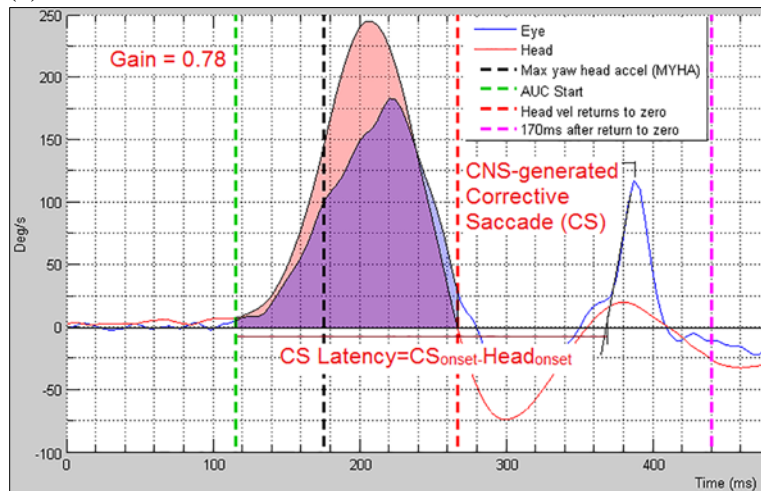
Figure 2.2: Gaze stability testing equipment and procedures.

(a) vHIT goggles.

(b) vHIT set up and procedures



(a)



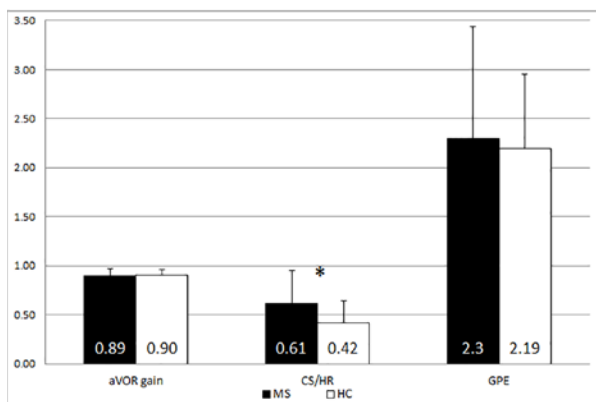
(b)

Figure 2.3: Variables of gaze stability. The eye velocity has been inverted for ease of comparison

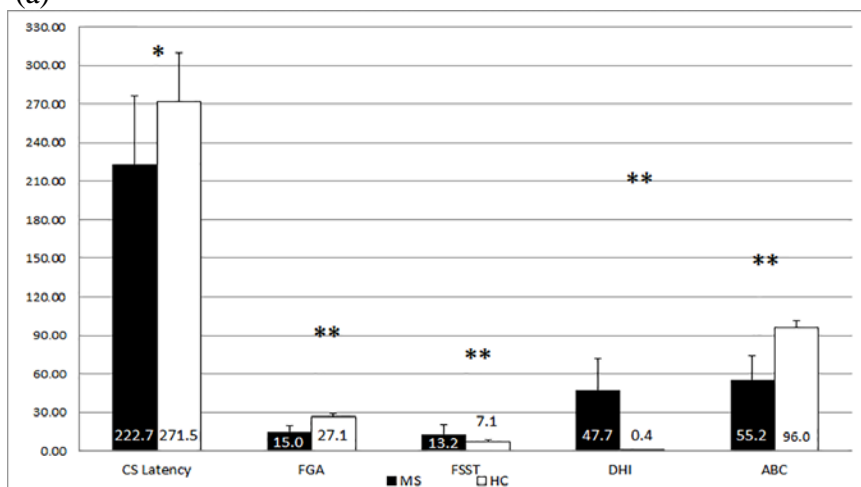
(a) HC: vHIT test result from a single HIT illustrating a normal aVOR gain (0.99) and no saccades

(b) MS: Experimental subject with decreased aVOR gain (0.78) and an overt saccade within 170ms of head velocity crossing zero

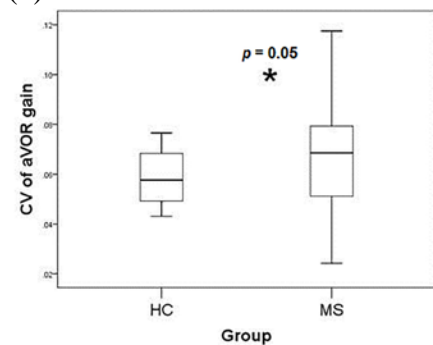
Abbreviations. MS: Multiple Sclerosis.



(a)



(b)



(c)

Figure 2.4. Group means and error bars.

(a): aVOR gain, CS/HR, GPE

(b): CS latency, FGA, FSST, DHI, ABC

(c): CV of aVOR gain

\*\* denotes significance at  $p < 0.001$ , one-tailed significance\* denotes significance at  $p \leq 0.05$ , one-tailed significance

Abbreviations. MS: Multiple Sclerosis; CS/HR: Compensatory Saccades per Head Rotation.

## CHAPTER 3

# TEST-RETEST RELIABILITY AND RESPONSE STABILITY OF GAZE STABILIZATION, POSTURAL SWAY, AND DYNAMIC BALANCE TESTS IN PERSONS WITH MULTIPLE SCLEROSIS AND CONTROLS

### Abstract

The psychometric properties of tests that assess the angular Vestibulo-Ocular Reflex (aVOR) and vestibulo-spinal reflex function are unknown in both healthy and patient subjects. We aimed to investigate the test-retest reliability and response stability of gaze stabilization, postural sway, and dynamic balance measures in Persons with MS (PwMS) and controls. Nineteen ambulatory PwMS at fall-risk and fourteen age-matched controls were recruited for cross-sectional analysis. Passive horizontal head impulses, static standing on an in-ground force platform, and dynamic balance were tested on two separate occasions. Gaze stabilization outcomes included (a) aVOR gain (ratio of eye to head velocity); (b) number of Compensatory Saccades per Head Rotation (CS/HR); (c) CS latency; (d) Gaze Position Error (GPE). Postural Sway outcomes included (e) Medio-Lateral (ML) sway amplitude; (f) Antero-posterior (AP) sway amplitude; (g) total sway path. Dynamic balance measures included (h) Functional Gait Assessment (FGA); (i) Four Square Step Test (FSST). Intraclass Correlation Coefficient [ICC(3,1)], Standard

Error of Measurement (SEM, SEM%), and Minimal Detectable Difference at 95% confidence level (MDD95, MDD95%) were calculated. In our sample, aVOR gain, CS/HR, and GPE demonstrated moderate reliability while each postural sway and dynamic balance measure demonstrated good reliability. Angular VOR gain, CS latency, and each postural sway and dynamic balance variable had low measurement error (SEM, SEM%), suggesting acceptable response stability. Low MDD95 and MDD95% values were seen for aVOR gain, FGA, and FSST, suggesting acceptable response stability such that a relatively smaller change in performance is needed to detect a real modification in these measures across repeated testing sessions. These results provide support for the use of these outcome measures for examination and treatment efficacy purposes.

### Introduction

Balance disorders are frequent in Persons with Multiple Sclerosis (PwMS),<sup>1</sup> with corresponding consequences such as falls, co-morbidities, decreased physical activity, and impaired quality of life.<sup>2,3</sup> Gaze and postural instabilities have been associated with balance impairments and increased fall-risk.<sup>2,4</sup> Gaze stabilization during head movements is a function of the Vestibulo-Ocular Reflex (VOR) and other oculomotor strategies which generate compensatory eye movements to maintain visual stability of a target.<sup>5,6</sup> Recently, the video-Head Impulse Test (vHIT) has been utilized to assess gaze stabilization,<sup>7</sup> and although the measurement accuracy of vHIT has been established,<sup>7,8,9</sup> there is limited data available on its reliability in PwMS or healthy individuals.

Postural instability is frequently examined by standing postural sway and clinical balance measures. Standing postural sway measures utilize Center of Pressure (COP)-

based findings on a force platform.<sup>10</sup> Impairments in standing postural sway have been associated with balance and gait impairments<sup>11, 12</sup> and are identified as important targets for functional recovery.<sup>13</sup> Clinical balance measures, on the other hand, include a variety of performance-based tests such as reaching, timed walking, and stair climbing tests. One such measure is the dynamic gait index, which has previously been studied in PwMS<sup>14, 15, 16</sup>; however, the reliability of a modified version, the Functional Gait Assessment (FGA), is currently unknown in PwMS. Similarly, very few studies have examined the Four Square Step Test (FSST) performance in PwMS.<sup>17, 18</sup> Since the FGA and FSST have been associated with fall-risk and balance deficits in people with vestibular disorders,<sup>19, 20</sup> there is a need to examine their reliability in PwMS.

Identification of reliability and response stability are critical to detect true differences between two sessions beyond that attributable to measurement error. The psychometric properties for measures of gaze stabilization (utilizing vHIT), postural sway (COP-based variables), and dynamic balance (FGA) are not established in PwMS. Although previously studied, further research is warranted on the reproducibility and response stability of FSST in a different setting. Therefore, to support the use of these outcome measures for examination and treatment efficacy purposes, we aimed to investigate the (i) test-retest reliability and (ii) stability of repeated responses for gaze stabilization, postural sway, and dynamic balance measures in PwMS as well as age-matched controls. We hypothesized that these measures would demonstrate at least moderate reliability and acceptable response stability in PwMS and controls.



## Methods

### Participants

Thirty-nine PwMS recruited from local neurologists and support groups were screened (Fig 3.1). Age-matched neurologically Healthy Controls (HC) were recruited from the community. The data presented for this study are part of a larger trial in which the sample size was determined from previously observed effect sizes for between-group differences in aVOR gain using vHIT.<sup>9</sup> Selection criteria for PwMS were: confirmed MS diagnosis; able to stand at least 30 seconds without support; Expanded Disability Severity Scale (EDSS) score of  $\leq 6.5$ ; fall-risk established by:  $\geq 2$  retrospective falls per year, activities-specific balance confidence score  $< 70$ , Berg balance test score  $< 44$ , or dizziness handicap inventory score  $> 59$ <sup>14</sup>; no history of exacerbations in the previous 3 months; no history of other peripheral or central nervous system injury or neuro-otologic condition besides MS; absence of internuclear ophthalmoparesis or ophthalmoplegia and absence of other orthopedic, cognitive, medical, or surgical limitations that may limit their participation in the study.

### Study procedures

Participants who met the inclusion criteria signed an institutional review board approved informed consent form and provided the medical, MS-related, and fall history via personal interviews. Thereafter, the fall-risk assessments to identify PwMS who met any one of the four above-mentioned fall-risk criteria were conducted. In all PwMS at fall-risk, we excluded persons with peripheral vestibular pathologies using a clinical vestibular examination comprised of oculomotor range of motion, bedside HIT, VOR

cancellation test, saccades, and test of skew.<sup>5</sup> Peripheral vestibular pathologies were screened for using an infrared video goggles system and examining for nystagmus at-rest, positive benign positional vertigo tests, and head-shake nystagmus. The consented participants subsequently underwent a physical therapist-administered neurological examination (EDSS).<sup>21</sup> The gaze stabilization, standing postural sway, and dynamic balance measurements were then conducted on a single day followed by a repeat assessment on a different day. The assessment days were separated by a gap of at least two days (Fig 3.1) and were conducted by the same assessor.

### Measures

Gaze stabilization was determined using the vHIT goggles (GN Otometrics, Denmark, Fig 3.2), which have been previously validated in people with aVOR deficits.<sup>7,</sup>  
<sup>8</sup> The experimenter administered horizontal (yaw) head impulses to each side in order to collect at least eight trials suitable for analysis. The detailed study procedure is described in Appendix A. The gaze stabilization variables (Fig 3.3) were: angular VOR (aVOR) gain, number of Compensatory Saccades per Head Rotation (CS/HR), CS latency, and Gaze Position Error (GPE). The aVOR gain was determined by dividing the de-saccaded eye velocity Area Under the Curve (AUC) by the head velocity AUC, beginning with the onset of the head impulse to the instant when head velocity reverted to zero.<sup>9</sup> The onset of head movement was preferentially determined by the methods described by MacDougall et al.<sup>9</sup> as the time point 60 msec prior to Maximal Yaw Head Acceleration (MYHA). The accuracy of this method was checked manually by visual inspection. In a few instances where the MacDougall et al.<sup>9</sup> technique inaccurately identified the onset,

the start of head movement was identified as the latest point in time when the head velocity rose above zero and continued to move in the intended direction. Although head rotations to both left and right directions were performed, the aVOR gain of the worst functioning side was utilized as the dependent variable. The CS/HR were manually counted for each head rotation and then averaged over the number of rotations. For investigative purposes, a CS was defined as a horizontal eye rotation occurring during the head rotation that assisted a deficient aVOR and occurred in the direction of the vestibular slow component.<sup>22</sup> The CS latency was calculated as the time duration between onset of head acceleration to onset of first identifiable CS. The GPE was measured by subtracting the eye position from target position when the head velocity returned to zero.

Standing postural sway was assessed using one AMTI OR6-7 series force platform (Advanced Medical Technologies Inc, Watertown, MA, USA). The kinetic (COP) data were sampled at 200Hz. Data were captured using Vicon Nexus (Vicon Motion Systems, Centennial, CO, USA). The detailed study procedure is described in Appendix A. The following postural sway variables were calculated over a 25-second interval of quiet stance: (a) Medio-Lateral (ML) sway amplitude, determined as the maximal excursion of COP in the ML direction; (b) Antero-Posterior (AP) sway amplitude, determined as the maximal excursion of COP in the AP direction; and (c) total sway path, determined as the cumulative COP excursion over the 25 seconds. Postural sway has previously been studied in PwMS.<sup>23, 24</sup>

Dynamic balance was examined using the FGA and the FSST. The FGA is a 10-item gait test with established reliability and validity that assesses stability during various

walking tasks on a marked 6-m (20-ft) length and 12-inch wide walkway.<sup>25, 26</sup> The FSST assesses an individual's ability to change directions while stepping. For this test, a square is formed with four canes resting flat on the floor and the subject is asked to step as fast as possible in each square.<sup>27</sup> The procedure was demonstrated and one practice trial was allowed. The fastest time of one trial from two completed trials was recorded in seconds. The reliability and validity of FSST has been established.<sup>18, 19, 27, 28</sup>

### Data reduction and analysis

The collected raw data from the vHIT were exported to custom software written in Matlab (Math-Works, Natick MA) for screening and analysis. Standardized screening measures were employed to discard trials with blinks and movement artifacts.<sup>29</sup> Briefly, trials were screened using the following criteria: visual inspection for appropriateness of eye and head movement; blink identification by either detecting a biphasic deflection of the eye in the lateral plot or an acute deflection in the pitch plot.<sup>29</sup> Kinetic data from Vicon Nexus were imported into Visual 3D (C-Motion Inc, Germantown, MD, USA) software for further analysis. The data were filtered using a lowpass, zero-phase shift, Butterworth filter at 20Hz based on visual inspection of the data and the results of a residual analysis.<sup>30</sup> SPSS version 23.0 (IBM Corporation, Armonk, NY) was used for all analyses.

Data for all dependent variables were examined collectively as well as separately for PwMS and controls. Test-retest reliability, which reflects the agreement between scores on each testing day, was assessed using the Intraclass Correlation Coefficient (ICC) with a 2-way mixed effects model (ICC(3,1)).<sup>31</sup> ICC point estimators were

interpreted using the following criteria: ICC <0.5 indicates poor, 0.5–0.75 moderate, and >0.75 good reliability.<sup>31</sup> Response stability was established by calculations of Standard Error of Measurement (SEM) and Minimal Detectable Difference with a confidence level of 95% (MDD95). The SEM was computed as  $SEM = SD \sqrt{1 - \text{estimated reliability coefficient}}$ , where SD is the pooled standard deviation of test–retest measures, while the MDD95 (i.e., measure of true change) was calculated as  $1.96 \times \sqrt{2} \times SEM$ .<sup>31</sup> The SEM and MDD95 values, expressed in the unit of measurement, describe the limits for change that can be considered above the threshold of measurement error and indicate a true change after treatment. The SEM% and MDD95% were also determined as a percentage of the mean to produce unit less indicators and allow for comparisons. SEM% and MDD95% <20% were considered as a conservative estimate of low measurement error and acceptable response stability.<sup>32</sup>

### Results

Nineteen PwMS met the inclusion criteria and participated. The MS Group comprised of 3M/16F with a mean  $\pm$  SD age=53  $\pm$  11.7yrs, falls/yr=4.2  $\pm$  3.3, and diagnosis duration= 16  $\pm$  11.4yrs, while the HC Group included 5M/9F with age=55  $\pm$  11.9yrs and falls/yr= 0.07  $\pm$  0.3 (Table 3.1).

In the overall study sample, gaze stabilization measures (aVOR gain, CS/HR, GPE) demonstrated moderate test-retest reliability (ICC range=0.54-0.65) except CS latency (ICC=0.17). The aVOR gain and GPE demonstrated moderate reliability in PwMS, while the aVOR gain and CS/HR demonstrated moderate reliability in HC. CS latency demonstrated poor reliability in both groups (Table 3.2).

The postural sway measures demonstrated good reliability (ICC range=0.91-0.98) with similar results seen for separate group analyses (Table 3.2). The dynamic balance measures demonstrated good reliability in the total sample (ICC range=0.89-0.98) with similar results seen for separate group analyses (Table 3.2).

Irrespective of the group, aVOR gain, CS latency, and all postural sway and dynamic balance variables exhibited low measurement error (SEM% <20) and acceptable response stability. Relative to controls, larger MDD95 estimates for CS/HR, postural sway measures, and FSST were seen in PwMS (Table 3.2). Angular VOR gain and FGA demonstrated low (<20%) MDD95%. Lastly, FSST demonstrated high MDD95% in persons with MS as compared to controls (27% versus 18%).

### Discussion

This study aimed to examine the psychometric properties of gaze stabilization, postural sway, and dynamic balance measures by assessing the test-retest reliability and response stability between two separate assessments in PwMS and controls. We determined that the majority of gaze stabilization measures demonstrated moderate test-retest reliability while the postural sway as well as dynamic balance measures showed good test-retest reliability. The aVOR gain, CS latency, and all postural sway and dynamic balance variables demonstrated SEM % <20, suggestive of acceptable response stability. The aVOR gain, FGA, and FSST showed low MDD95% suggesting acceptable response stability. The SEM and MDD values obtained from this study should enhance the interpretation of gaze and postural stability changes seen posttreatment in PwMS and older adults during intervention research and during clinical decision making.

### Test-retest reliability: ICC

The aVOR gain was found to be a moderately reliable outcome for PwMS and HC in this study (Table 3.2). Its ‘moderate’ ICC value is likely related to within-individual variability in aVOR gain. While hand placement technique<sup>33</sup> and head thrust velocities<sup>34</sup> have been identified as sources of variability, we used a consistent hand placement technique for all trials. Additionally, the average head velocities administered on the two assessment days were similar ( $186.80 \pm 18.21$  degrees/s on Day 1 versus  $187.60 \pm 17.65$  degrees/s on Day 2). We also demonstrated moderate reliability for other gaze stabilization measures (CS/HR and GPE). To our knowledge, this is the first study to report the test-retest reliability of horizontal vHIT in PwMS as well as HC using the GNOtometrics system. These results concur with a previous study of healthy young adults using a different device.<sup>35</sup> Future studies should investigate the sources of variability in gaze stabilization assessments and determine ways to minimize it.

Good reliability for postural sway outcomes was found in all study participants. These findings are consistent with previous work.<sup>36-38</sup> In addition, dynamic balance measures exhibited good test-retest reliability in all study participants. Similar results have been demonstrated by previous studies in individuals with stroke<sup>26</sup> and Parkinson’s disease<sup>39</sup> (ICC>0.90), emphasizing the usefulness of FGA in assessing dynamic stability in neurological populations. This study demonstrated better test-retest reliability of FGA in PwMS compared to healthy controls. Our findings are consistent with the FSST ICC values of 0.92 and 0.98 that have been previously reported in ambulant PwMS and elderly, respectively.<sup>18, 27</sup> Taken together, these results support the use of postural sway and dynamic balance assessments in clinical practice and as behavioral outcome

measures in research trials. However, such results should be combined with the information on measurement error of these instruments.

#### Response stability: SEM, MDD95 and SEM%, MDD95%

In this study, information from response stability metrics allows the clinician or researcher to interpret an observed change in an outcome as a potential product of measurement error or as a meaningful change in vestibular physiology or postural behavior. This study found low measurement error (SEM, SEM%) for aVOR gain, CS latency, all postural sway, and dynamic balance variables. Low MDD95 and MDD95% values were seen for aVOR gain, FGA, and FSST only.

Regardless of group membership, aVOR gain demonstrated acceptable response stability, suggesting that a relatively small magnitude change is required to demonstrate a real change in performance as opposed to the other gaze stabilization measures (Table 3.2). The contributors to increased measurement error in gaze stabilization measures may include the location and severity of demyelination; the stability and degree of vestibular dysfunction in the subject being tested; age; the testing instrumentation; and the testing technique. Further research is warranted to characterize common sources of measurement error and recommend steps to minimize this error for diagnostic, prognostic, and rehabilitative purposes.

Low error (SEM% <20%) in the postural sway and dynamic balance measures suggests acceptable response stability for research and clinical practice. Amongst the COP-based variables, total sway path consistently demonstrated the lowest MDD95 estimates and percent values suggesting less measurement error than other outcomes.



Previous studies have found similar results in individuals with stroke<sup>38</sup> and healthy individuals.<sup>36</sup> We also determined a range of MDD95% estimates (<50%, Table 3.2) for postural sway variables, indicating that further research is still needed to appropriately define population-specific outcomes of postural sway. This study found better response stability for FGA and FSST in both groups as compared to previous reports.<sup>18, 26</sup> Less response stability for the FSST was seen in PwMS as compared to controls, which suggests greater variability in FSST performance in those with neurologic deficits (Table 3.2). Clinically, this implies that to identify a real performance modification, a greater change is required in PwMS than neurologically healthy individuals. Although there is no consensus on the acceptable amount of measurement error,<sup>32</sup> these findings support the use of some of these balance assessments in clinical and research settings for PwMS as well as older adults.

### Limitations

Small sample size and heterogeneity may have influenced the results; therefore, a larger study including homogenous groups of older adults and PwMS is warranted to support the utility of these gaze assessments in clinical practice. In addition, the current reliability data may not be generalized to other populations with neurological and vestibular conditions. By design, this study chose to assess the test-retest reliability with a single rater and across different days; therefore, these results cannot be applied towards within-day assessments and multiple raters.

### Conclusions

The present study found moderate reliability of gaze stabilization measures and good reliability of postural sway and dynamic balance measures in PwMS as well as age-matched controls. While aVOR gain, FGA, and FSST may be reliable and stable across repeated testing sessions, a relatively larger change in performance may be needed to detect real change for the remainder of the gaze stabilization and COP-based measures.

## Appendix

### Gaze stabilization assessment procedures

Subjects were seated and asked to fixate their eyes at a target on the wall at a meter distance in dim light. Passive horizontal (yaw) head impulses (amplitude  $10^{\circ}$ – $20^{\circ}$ ) to each side were administered by a single experimenter. The range for peak head velocity of the impulses was from  $120^{\circ}$  to  $350^{\circ}$ /second. The eye velocity for the right side was assessed using a small, high-speed, lightweight digital video camera with a sampling rate of 250Hz. An elastic strap was utilized to minimize the slippage of the camera relative to the head. A mirror reflected the image of right eye to the camera. A rate sensor measured the head velocity (the stimulus). The camera, mirror, and rate sensor were assimilated into a spectacle frame. The manufacturer's registered software was used to capture and store the head and eye velocity data (the response).

### Postural sway assessment procedures

Subjects stood quietly with their head facing forward, arms at their sides, barefooted, and eyes open. The heels were 10cm apart and the toes were angled outward approximately 20 degrees. The participant's height and weight were recorded. Butcher block paper was attached to the force platform to trace the participant's feet to ensure the same starting position across all trials. The COP data, sampled at 200Hz, were recorded and therefore subjected to filtering and postprocessing procedures. Ten trials for each subject were conducted and each trial lasted 25 seconds.

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Table 3.1. Descriptive statistics<sup>a</sup>.

	MS (n=19)	HC (n=14)
Gender (M/F)	3/16	5/9
Age	53.4 ± 11.66 (47.80-59.04)	54.64 ± 11.88 (47.78-61.50)
EDSS (min-max)	4.95 ± 1.0 (3.5-6.5)	-
Diagnosis Duration	16 ± 11.44 (10.49-21.51)	-
Berg Score	46.37 ± 7.10 (42.94-49.79)	55.4 ± 1.26 (54.49-56.31)
falls/yr	4.16 ± 3.35 (2.54-5.76)	0.07 ± 0.27 (-0.08-0.23)

a All values are mean (standard deviation)/95% confidence interval unless otherwise indicated.

Abbreviations: MS, Multiple Sclerosis.



Table 3.2. Reliability (ICC and measurement error) in people with MS and controls.

Variable	All subjects							MS							Controls						
	Mean day 1	Mean day 2	ICC (3,1) [95% CI]	SEM	SEM%	MD D95	MDD9 5%	Mean day 1	Mean day 2	ICC (3,1) [95% CI]	SEM	SEM%	MD D95	MDD9 5%	Mean day 1	Mean day 2	ICC (3,1) [95% CI]	SEM	SEM%	MD D95	MDD9 5%
<i>Gaze stability</i>																					
aVOR gain	0.89	0.92	0.65 [0.40 - 0.81]	0.04	4.52	0.11	12.54	0.89	0.92	0.72 [0.40 - 0.88]	0.04	4.50	0.11	12.47	0.90	0.91	0.50 [-0.02 - 0.81]	0.04	4.59	0.12	12.72
CS/HR	0.53	0.42	0.54 [0.25 - 0.74]	0.22	45.58	0.60	126.35	0.61	0.49	0.42 [-0.03 - 0.73]	0.27	48.97	0.74	135.73	0.42	0.33	0.75 [0.39 - 0.91]	0.12	31.83	0.33	88.24
CS Latency (ms)	243.83	256.12	0.17 [-0.22 - 0.51]	48.74	19.50	135.09	54.04	222.71	248.54	0.01 [-0.51 - 0.52]	48.47	20.57	134.35	57.02	271.45	264.79	0.04 [-0.51 - 0.56]	53.22	19.85	147.53	55.02
GPE (degrees)	2.25	2.03	0.59 [0.32 - 0.77]	0.64	29.64	1.76	82.15	2.30	2.10	0.71 [0.39 - 0.88]	0.61	27.76	1.69	76.94	2.19	1.95	0.23 [-0.32 - 0.67]	0.69	33.42	1.91	92.63
<i>Postural sway</i>																					
ML amplitude (mm)	18.80	17.80	0.93 [0.87 - 0.97]	3.05	16.65	8.45	46.15	24.00	22.60	0.92 [0.80 - 0.97]	3.63	15.57	10.06	43.17	9.70	9.50	0.79 [0.39 - 0.94]	1.68	17.54	4.67	48.62

Table 3.2. Continued.

Variable	All subjects								MS								Controls						
	Mean day 1	Mean day 2	ICC (3,1) [95% CI]	SEM	SEM%	MD D95	MDD 95%		Mean day 1	Mean day 2	ICC (3,1) [95% CI]	SEM	SEM%	MD D95	MDD 95%		Mean day 1	Mean day 2	ICC (3,1) [95% CI]	SEM	SEM%	MD D95	MDD 95%
AP amplitude (mm)	30.30	28.80	0.91 [0.82 - 0.95]	4.31	14.57	11.94	40.40		36.10	34.10	0.87 [0.70 - 0.95]	5.14	14.64	14.24	40.58		20.30	19.60	0.90 [0.68 - 0.97]	2.11	10.57	5.84	29.29
Total sway path (mm)	384.20	395.60	0.98 [0.97 - 0.99]	36.95	9.48	102.43	26.27		473.20	484.10	0.98 [0.96 - 0.99]	41.94	8.76	116.24	24.29		230.60	242.70	0.76 [0.34 - 0.93]	24.62	10.40	68.25	28.84
<i>Dyna mic balance</i>																							
FGA	20.12	20.58	0.98 [0.96 - 0.99]	1.02	5.04	2.84	13.96		15.00	15.47	0.95 [0.88 - 0.98]	1.00	6.56	2.77	18.19		27.07	27.50	0.82 [0.53 - 0.94]	1.03	3.78	2.86	10.47
FSST (s)	10.51	10.84	0.89 [0.78 - 0.94]	1.34	12.60	3.73	34.92		13.20	14.00	0.87 [0.68 - 0.95]	1.34	9.86	3.72	27.33		7.05	6.78	0.93 [0.80 - 0.98]	0.46	6.59	1.26	18.26

Abbreviations: MS, Multiple Sclerosis; CI, Confidence Interval of the difference; CS/HR, Compensatory Saccades per Head Rotation; MDD95, Minimal Detectable Difference with a confidence level of 95%

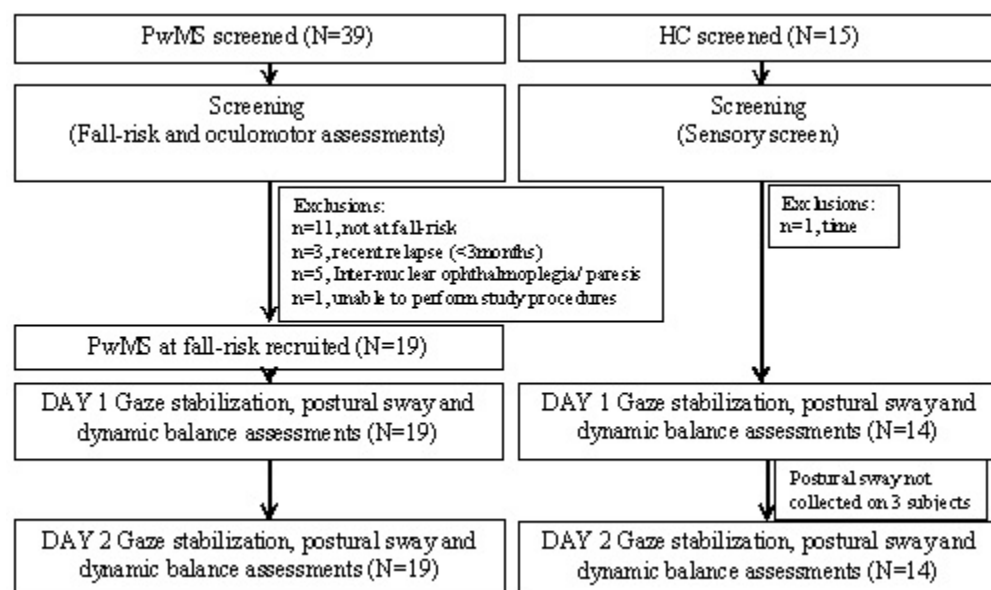


Figure 3.1. Diagram illustrating the flow of participants through the trial.



Figure 3.2. vHIT equipment.

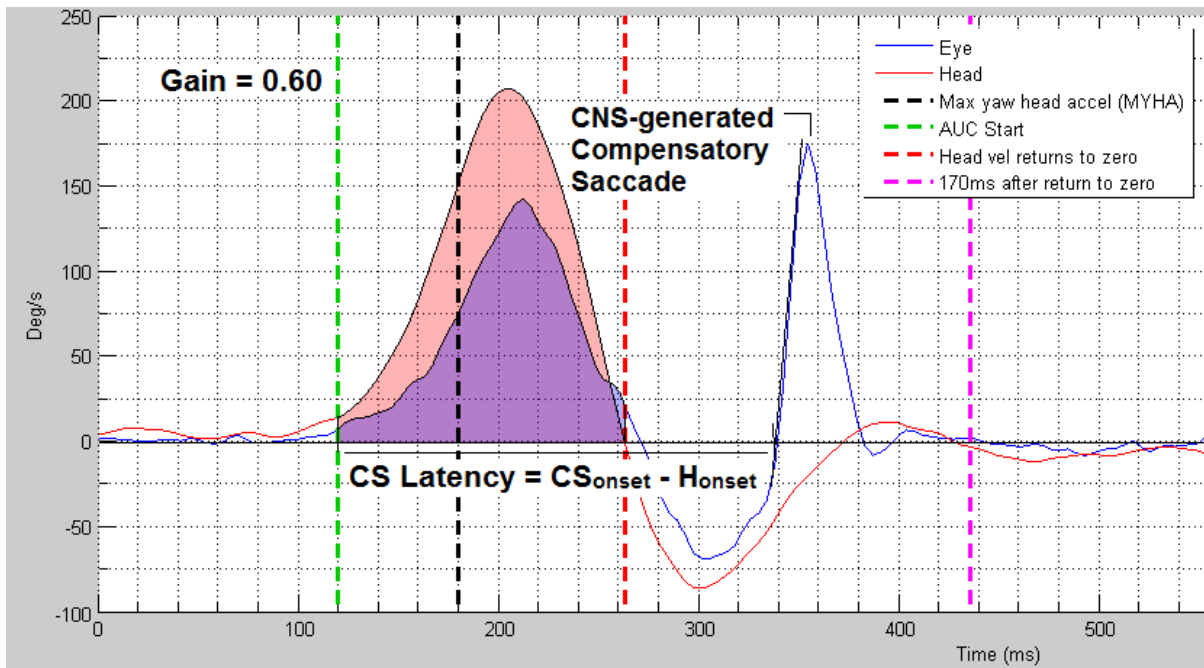


Figure 3.3. Gaze stabilization measures. The eye velocity has been inverted for ease of comparison. Experimental subject with MS demonstrating decreased aVOR gain (0.60) and an overt saccade within 170ms of head velocity crossing zero.

Abbreviations: CNS, Central Nervous System;  $H_{onset}$ , Onset of head acceleration; MS, Multiple Sclerosis.

## CHAPTER 4

# ADAPTATIONS IN GAZE, GALVANIC-INDUCED POSTURAL SWAY, BALANCE, AND PARTICIPATION AFTER HOME-BASED TRAINING IN PEOPLE WITH MULTIPLE SCLEROSIS

### Abstract

Demyelination of vestibulo-ocular and -spinal pathways in the brainstem and cerebellum may adversely affect gaze, posture, and balance in People with Multiple Sclerosis (PwMS), but the effect of Gaze and Postural Stabilization (GPS) training programs remains unexplored. This study investigated the effects of GPS training on measures of gaze stability, galvanic-induced postural sway, dynamic balance, and participation in PwMS. Nineteen ambulatory PwMS at fall-risk consented and participated. Outcomes included gaze stability [angular Vestibulo-Ocular Reflex (aVOR) gain, number of Compensatory Saccades per Head Rotation (CS/HR), CS latency, Gaze Position Error (GPE)]; galvanic-induced postural sway [Medio-Lateral (ML) sway amplitude, time latency to restabilization]; dynamic balance [Functional Gait Assessment (FGA), Four Square Step Test (FSST)]; and participation [Activities-specific Balance Confidence scale (ABC), Dizziness Handicap Inventory (DHI)]. The home-based GPS training comprised of two horizontal gaze and two postural stability exercises performed for 20 minutes/day for 2 weeks. Separate Wilcoxon signed rank tests were conducted to

examine for changes over the course of training. Significant differences ( $p < 0.05$ ) in aVOR gain, CS/HR, ML sway amplitude, FGA, FSST, ABC, and DHI scores were found. The GPS training resulted in changes across the entire spectrum of outcome measures highlighting its efficacy in PwMS at fall-risk. Gaze stability was achieved by recruiting substitutive oculomotor strategies (CS/HR) while postural stability by sway response adaptations. Future research should examine the efficacy of training using a randomized clinical trial design, examine skill transfer (passive versus active head rotations), and test for long-term retention of gaze and postural stability improvements in PwMS.

### Introduction

Clinical symptoms of dizziness and imbalance may occur due to deficits in perception and integration of vestibular sensations as well as defects in motor efferent responses in Persons with Multiple Sclerosis (PwMS).<sup>1,2</sup> The Vestibulo-Ocular Reflex (VOR) and Vestibulo-Spinal Reflex (VSR) are essential sensorimotor mechanisms required to maintain gaze and postural stability during Activities of Daily Living (ADLs).<sup>2</sup> The angular VOR (aVOR) and other compensatory oculomotor mechanisms stabilize gaze and maintain clear vision during angular head motions. The VSR, on the other hand, plays a key role in maintaining head and body stability during static and dynamic postures and movements. The demyelination of brainstem and cerebellar pathways may adversely affect the aVOR and VSR physiology, thereby altering gaze, posture, and dynamic balance function in MS.<sup>3</sup> A few studies have reported altered vestibular function, in the form of impairments in oculomotor function, posturography, and

vestibular-evoked potentials in PwMS.<sup>4-6</sup> However, the effect of rehabilitation interventions targeted to improve gaze, posture, and balance still remains less investigated in PwMS.<sup>7,8</sup> Furthermore, no study has examined the mechanisms behind changes in oculomotor behavior after rehabilitation interventions in PwMS.

Vestibular rehabilitation therapy is recognized as a widely accepted intervention for individuals with balance and vestibular disorders.<sup>9-11</sup> It includes a range of exercises including adaptation, substitution, and habituation to target aVOR and VSR functions and therefore improve gaze and postural stability. Adaptation strategies aim to restore the motor behavior of aVOR and VSR mechanisms, whereas substitution strategies recruit alternative motor mechanisms to enhance the deficient aVOR and VSR output.<sup>2,12</sup> Habituation techniques, on the other hand, include repeated performance of a task to habituate, or decrease sensitivity to a stimulus.<sup>2</sup> The efficacy of vestibular rehabilitation has been demonstrated in people with central vestibulopathies<sup>13</sup> and concussion<sup>14</sup>; however, very few studies have examined its benefits in PwMS.<sup>7,8,15</sup> Previous work has demonstrated improvements in static balance<sup>8</sup> and dizziness handicap after vestibular intervention in four PwMS,<sup>8,15</sup> though limited sample size restricts the relevance of these results to a wider group of PwMS. Hebert et al.<sup>7</sup> also found improvements in fatigue, upright posture, and dizziness after vestibular therapy in PwMS. While these studies suggest potential benefits of vestibular interventions in PwMS, the effectiveness of its major constituent – the Gaze and Postural Stabilization (GPS) training – has not been well-established. In addition, balance interventions currently utilized in MS rehabilitation frequently include dynamic activities that require head and eye movement, but the effect of GPS training on detailed measures of gaze, posture, and balance control and



community participation remain less studied. This study aimed to investigate the effects of self-administered GPS training on gaze stability, galvanic-induced postural sway, dynamic balance, and self-report participation measures in PwMS at fall-risk. Based on previous research, we hypothesized that PwMS will demonstrate significant improvements in these measures posttraining.

## Methods

### Participants

Thirty-nine PwMS at fall-risk from local neurology clinics and support groups were screened (Figure 4.1). Based on previously observed effect sizes for passive aVOR gain after training<sup>16</sup> and accounting for 15% attrition, we determined that 15 PwMS will provide adequate power ( $1 - \beta = 0.80$ ) to demonstrate changes after training. The inclusion criteria were: confirmed MS diagnosis, ability to stand at least 30 seconds without support, Expanded Disability Severity Scale (EDSS)<sup>17</sup> score  $\leq 6.5$ , and fall-risk recognized by meeting one of the following criteria:  $\geq 2$  retrospective falls per year, Berg Balance Test (BBT) score  $<44$ , Activities-specific Balance Confidence (ABC) score  $<70$ , or Dizziness Handicap Inventory (DHI)  $> 59$ .<sup>18</sup> Potential participants were excluded if they demonstrated internuclear ophthalmoparesis or ophthalmoplegia, history of other central or peripheral nervous system disorder or neuro-otologic condition besides MS, a history of recent ( $<3$  months) relapse, or demonstrated medical, surgical, orthopedic, or cognitive limitations that would limit participation with the study procedures.

### Study procedures

All participants who met the inclusion criteria signed the institutional review board approved informed consent. The medical, MS-related, and fall history were gathered by personal interviews, following which the fall-risk measures were performed. In all PwMS at fall-risk, a clinical vestibular examination was conducted to confirm the absence of peripheral vestibular pathologies. This exam included the oculomotor range of motion, saccades, testing for skew deviation, clinical head thrust test, and the observation of resting, gaze-evoked, and positional nystagmus using an infrared video goggles system. The recruited individuals underwent a neurological examination for EDSS score determination.<sup>17</sup> On a separate day (pretraining), gaze stability, galvanic-induced postural sway, and dynamic balance were assessed (Figure 4.1). Participants then completed a home-based GPS training regime for 2 weeks. To ensure compliance, video chat sessions, phone calls, or in-person visits were provided by the researchers once per week. After the intervention, the outcomes were re-assessed (posttraining). Pre- and posttraining outcomes were utilized to examine changes in gaze stability, galvanic-induced postural sway, dynamic balance, and participation measures after the GPS training. The same investigator assessed all participants at each time point.

### Measures

This study utilized outcomes spanning the World Health Organization's International Classification of Function, Disability, and Health (ICF) model to examine the extent of differences pre- versus post-GPS training. The outcomes therefore encompassed the 3 ICF domains – body structure and function, activity, and

participation.<sup>19</sup>

*The body structure and function domain* was quantified by measures of gaze stability and galvanic-induced postural sway. Gaze stability was assessed by using the video Head Impulse Test (vHIT) goggle system (GN Otometrics, Denmark). The validity of vHIT has been established in people with aVOR deficits.<sup>20, 21</sup> A single examiner administered the passive horizontal (yaw) head impulses to the left and right side in order to collect at least eight trials on each side. The detailed procedure is outlined in Appendix A (see Supplemental Digital Content 1). The gaze stability variables included the: aVOR gain, number of Compensatory Saccades per Head Rotation (CS/HR), CS onset latency, and Gaze Position Error (GPE) (Figure 4.2). The aVOR gain was determined by dividing the de-saccaded eye velocity Area Under the Curve (AUC) by the head velocity AUC, beginning with the onset of the head impulse to the instant when head velocity reverted back to zero.<sup>22</sup> The onset of head movement was preferentially defined as the time point 60 msec prior to attaining Maximal Yaw Head Acceleration (MYHA).<sup>22</sup> Visual examination of the head velocity traces established the accuracy of this method. Upon visual inspection, however, a few instances were discovered where the 60 msec method erroneously identified the head onset. For those few instances, the head onset was determined as the last time point when the head velocity crossed zero and continually moved in the intended direction. Although head rotations to both left and right sides were performed, the aVOR gain of the worst functioning side was utilized as the dependent variable. The CS/HR were manually counted per head rotation and were averaged for the total number of head rotations. A CS was defined as a horizontal eye rotation, occurring either during the head rotation or within 170 milliseconds after head velocity reached

zero, which assisted a deficient aVOR and occurred in the direction of the vestibular slow component (Figure 4.2).<sup>23</sup> The CS latency was calculated as the duration (milliseconds) between onset of head velocity to onset of first detectable CS. The GPE was measured by subtracting the eye position from target position at the completion of the head movement.

The Galvanic Vestibular Stimulation (GVS) was used to deliver a vestibular sensory illusion that elicited postural sway via the VSR.<sup>24, 25</sup> It was delivered using an isolated constant current stimulator (Grass Technologies, West Warwick, RI, USA) and the sway was measured by an AMTI OR6-7 series force platform (Advanced Medical Technologies Inc, Watertown, MA, USA). For each GVS trial on each participant, a 1.5 mA, 50Hz bipolar GVS was delivered for 500 milliseconds through electrodes applied over the bilateral mastoid processes with the cathode on the left side. For all trials, participants wore a harness and were provided a spotter to ensure safety. The Center Of Pressure (COP) position was derived from the force plate and sampled at 200 Hz. A custom-written Labview program (National Instruments Corporation Austin, TX, USA) was used to randomly trigger the GVS. The detailed procedure is outlined in Appendix A (see Supplemental Digital Content 1). Data were collected using Vicon Nexus (Vicon Motion Systems, Centennial, CO, USA). The variables of galvanic-induced postural sway were Medio-lateral (ML) sway amplitude and the time latency to restabilization after a vestibular sensory illusion, i.e., the GVS (Figure 4.3). The ML sway amplitude was determined as the maximal excursion of COP in the ML direction within a second from GVS onset. For the time latency to restabilization, the coefficient of variation of COP was calculated for 1-second prior to the GVS onset and was compared point by point with the coefficient of variation of COP for twenty 1-second epochs created after the

stimulus. The latency was determined as the time in seconds when the coefficient of variation of COP after the GVS returned to a similar or lower pre GVS value for two consecutive 1-second epochs. Galvanic-induced postural sway task has previously been utilized in healthy individuals as well as people with vestibular failure as a measure of VSR and postural stability.<sup>25</sup>

***The activity domain*** was assessed by measures of dynamic balance, the Functional Gait Assessment (FGA), and the Four Square Step Test (FSST). The FGA is a 10-item gait test that assesses dynamic stability during walking on a marked 6-m (20-ft) length and 12-inch wide walkway. Each item is rated 0 (unable to perform) to 3 (performed without difficulty) and higher scores indicate greater balance. The reliability and validity of FGA has been established.<sup>26</sup> The FSST is a test of dynamic balance that assesses an individual's ability to change directions while stepping. A square is formed with 4 canes resting flat on the floor and the subject is asked to step as fast as possible in each square.<sup>27</sup> The test procedure was demonstrated and one practice trial was allowed. The fastest time of 1 trial from 2 completed trials was recorded in seconds. Lower scores indicated greater balance. The reliability and validity of FSST has been established.<sup>28</sup>

***The participation domain*** was measured by two self-report instruments, the ABC and DHI. The ABC is a 16-item self-reported measure of balance confidence in performing various ADLs. Each question requires an individual to grade himself on a scale of 0 to 100 percent for their level of confidence<sup>29</sup> and higher scores indicate greater balance confidence. The average score for all 16 items was utilized as the dependent variable. The reliability and validity of ABC has been studied in PwMS<sup>18,30</sup> and it is considered an accurate predictor of falls in PwMS.<sup>31</sup> The DHI is a 25-item self-

assessment inventory designed to evaluate the self-perceived handicap imposed by dizziness or unsteadiness. The scale is comprised of 3 domains: functional, physical, and emotional. The total summed score ranges from 0 to 100 and was utilized in this study, with higher scores indicating greater handicap. The reliability and validity of DHI has been established in PwMS.<sup>18, 30</sup>

### Intervention

The GPS training focused on providing repeated exposure to error signals (retinal slip and postural perturbation) in the form of gaze and postural stability exercises that typically induce alterations in aVOR and VSR mechanisms, respectively. The training volume was derived from previous work which documented the appropriate dosage to elicit gaze and postural improvements in people with bilateral vestibular hypofunction.<sup>32</sup> For gaze stability, subjects were instructed in a home-based exercise program of two sitting horizontal gaze stabilization exercises, 4 times/day for a total of 20 minutes/day for 2 weeks. For postural stability, subjects were instructed in a home-based exercise program of two standing postural stabilization exercises on solid or compliant surfaces with their eyes open or closed, 4 times/day for a total of 20 minutes/day for 2 weeks. See Table 4.1 for the exercise progression. The initial difficulty of the exercises was individually determined by the research staff based on each participant's level of disability.

### Data reduction and analysis

The collected raw data from the vHIT were exported to custom software written in Matlab (Math-Works, Natick MA) for screening and analysis. Standardized screening measures were employed to discard trials with blinks and movement artifacts.<sup>33</sup> Briefly, trials were screened for inclusion using the following criteria: visual inspection for appropriateness and smoothness of eye and head movement; blink identification by either detecting a biphasic deflection in lateral eye movement velocity trace or an acute deflection in pitch eye movement velocity trace. The COP data from Vicon Nexus were imported into Visual 3D (C-Motion Inc, Germantown, MD, USA) software for further analysis. The kinetic data were filtered using a lowpass, zero-phase shift, Butterworth filter at 20Hz based on visual inspection of the data and the results of a residual analysis.<sup>34</sup>

Descriptive statistics were conducted to identify the presence of outliers and to test the assumptions of normality. Since the assumptions were not met, separate Wilcoxon signed-rank tests were conducted to analyze the pre- to posttraining differences in each of the dependent variables. Measures of within-group effect sizes were calculated for each dependent variable using the effect size estimate,  $r$ . The level of significance was set at 0.05.

### Results

The entire sample consisted of 16 women and 3 men with MS; mean (range) age = 53.4 yrs (35.0 – 73.0) and EDSS = 4.9 (3.5 – 6.5) (Table 4.2). Sixty-eight percent of individuals reported no use of assistive devices, 16 percent reported unilateral assistance,

and the rest reported bilateral assistance. Four individuals dropped out from the study due to sickness ( $n=2$ ), family problems ( $n=1$ ), and time ( $n=1$ ) and were excluded from the final pre-post analysis which was consequently comprised of 15 PwMS.

Participants demonstrated significant differences in aVOR gain ( $p=0.039$ ) and CS/HR ( $p=0.020$ ). As a group, they demonstrated decreased median aVOR gain from pre- to posttraining examinations. During this same time period, the median number of CS/HR increased. No significant pre- to posttraining differences were observed in CS latency (effect size,  $r=0.32$ ) and GPE ( $r=0.29$ ) (Table 4.3 and Figures 4.4 (a) and (b)). Participants demonstrated significant differences in the ML sway amplitude ( $p=0.018$ ). As a group, they demonstrated decreased median ML sway amplitude from pre- to post-training. No significant differences were observed in time latency to restabilization ( $r=0.07$ ) (Table 4.3 and Figures 4.4 (a) and (b)).

Participants demonstrated significant differences in FGA ( $p=0.0005$ ) and FSST ( $p=0.0005$ ). As a group, they demonstrated increased median FGA scores and decreased median FSST scores from pre- to posttraining (Table 4.3 and Figures 4.4 (a) and (b)). Participants demonstrated significant differences in ABC ( $p=0.002$ ) and DHI ( $p=0.0015$ ). As a group, they demonstrated increased median ABC scores and decreased median DHI scores from pre- to posttraining (Table 4.3 and Figures 4.4 (a) and (b)).

### Discussion

Dynamic activities using head and eye movements are routinely employed in balance interventions for PwMS, but the effect of GPS training on gaze, posture, and balance control is not well understood. We hypothesized that the self-administered GPS



training will improve gaze stability, galvanic-induced postural sway, dynamic balance, and self-report participation in PwMS at fall-risk. This study demonstrated improvements across the entire spectrum of outcome measures after training with the exception of aVOR gain, highlighting its efficacy in PwMS. With the GPS training, PwMS achieved gaze stability by increasing the recruitment of CS/HR, i.e., substitution strategies. The improvements seen in postural response, dynamic balance, and self-report outcomes suggest that adaptation and habituation strategies may also be present after training.

#### Alterations of gaze stability

The present study is the first to examine changes in gaze stability after a specific GPS intervention in PwMS. We found that in order to maintain clear vision, PwMS demonstrated increased reliance on substitutive oculomotor strategies by generating more CS/HR rather than improving aVOR gain output. The recruitment of CS/HR has previously been identified as an effective strategy to improve gaze stability and oscillopsia.<sup>12</sup> This was further evident by the lack of improvement in aVOR gain observed in our sample after training, indicating that a substitutive strategy to achieve gaze stability was instead in place. Despite the decrease, the median aVOR gain was within previously documented normative limits<sup>35</sup> and may not indicate a clinically important reduction. The lack of improvement in aVOR gain may suggest either a diminished ability of PwMS to adapt to high head rotation velocities or the insufficient dosage of GPS training provided to study participants. This lack of adaptive ability may be explained by age,<sup>36</sup> presence of demyelinating lesions in the cerebellum,<sup>2</sup> or the inefficacy of an active gaze stability training to produce passive aVOR gain adaptations

indicative of context specificity of the training.<sup>2, 23</sup> Although decreased median latency of CS onset was demonstrated by PwMS after training (effect size = 0.32), the results failed to reach significance due to small sample size. Similarly, nonsignificant changes in GPE were observed, which can be attributed to either of the following: the presence of covert saccades during head rotations resulting in gaze overshoot or by definition of how we calculated GPE where the overt saccades were not included into our GPE calculations if they occurred within the 170msec duration after head velocity returned to zero. In summary, this study found that PwMS achieved gaze stability by synthesizing more CS/HR at potentially shorter onset latencies after a GPS intervention.

#### Alterations of postural stability and dynamic balance

This study also demonstrated a reduction in the amplitude of the ML postural sway response to a vestibular illusion after GPS training in PwMS. Although we lacked a control group for comparison, these findings are consistent with previous studies that have demonstrated improvements in upright balance in PwMS,<sup>7</sup> people with concussion,<sup>14</sup> and chronic unilateral vestibular disorders<sup>37</sup> after vestibular interventions. Interestingly, the time taken to restabilize after GVS did not change in PwMS, suggesting that the response to the GPS training affected the spatial aspects of participants to a greater degree than the temporal aspects.

Clinical changes in dynamic balance performance (FGA and FSST) after the GPS intervention were found as well such that the dynamic balance improved after training. Given the predictive validity of the FGA, this suggests a potential reduction in fall-risk of our sample. Although the efficacy of GPS training on FGA and FSST was not known in

PwMS prior to the present investigation, the effect of similar interventions had been studied on other measures of balance. Previous research has shown improvements in BBT,<sup>8, 38</sup> dynamic gait index,<sup>38</sup> and walking distance<sup>7</sup> after vestibular therapy. Findings from previous work in conjunction to the current study suggest that GPS interventions may produce generalization of sensorimotor strategies that improve the performance of dynamic postural tasks.

#### Clinical implications: balance confidence and dizziness handicap

Regardless of the varied response of body structure and function and activity measures, there was a consistent improvement in the self-report participation measures following the GPS training. From a clinical perspective, the mechanisms of aVOR and VSR changes are less meaningful than the subjective improvements in balance confidence and dizziness handicap. The effect of specific GPS exercises on balance confidence has not been previously investigated in PwMS; however, a combined motor and balance training produced no changes.<sup>38</sup> The significant changes observed in this study may be due to the unique exercise regime which might have been more effective than a traditional balance training program. Improvements in dizziness handicap observed in the current study may suggest a habituation mechanism to the observed improvement. Such results are similar to previous work,<sup>7, 8, 15</sup> therefore highlighting the utility of a GPS intervention in decreasing the impact of dizziness in PwMS at fall-risk.

### Limitations and Directions for Future Research

Due to the pilot nature of this investigation, generalizability is limited based on the sample size and the lack of a control group. Future studies should examine the efficacy of different vestibular and balance treatment approaches in a larger group of PwMS utilizing randomized clinical trial methods. By design, we measured gaze stability function by examining responses to passive head thrusts despite the fact that the GPS program had participants perform active head thrusts for training. Future studies should therefore examine the benefits of GPS training on active gaze stability measures such as the dynamic visual acuity. Lastly, this study only examined participants immediately after a 2-week training regime. Future research should compare varied durations of training and examine participants following a period of no treatment.

### Conclusions

People with MS at risk of falls demonstrated improvements in gaze and postural stability following the GPS intervention. Regardless of the effects on aVOR and VSR measures, PwMS in this study experienced improved dynamic balance function, improved balance confidence, and reduced dizziness handicap. Future research should further investigate the benefits of GPS training in comparison to controls and with additional outcomes such as the active gaze stability measures.

## Appendix

### Gaze stability assessment procedures

In sitting, participants were asked to fixate their gaze at a target on the wall in dim light which was a meter distance away. An experimenter administered passive horizontal (yaw) head impulses of 10°–20° amplitude to the left and right sides. The peak velocity of the head impulses ranged from 120° to 350°/second. The right eye velocity was measured by a small, high-speed digital video camera with a sampling rate of 250Hz. The image of the right eye was reflected by a mirror on to the camera. A rate sensor measured the head velocity (the stimulus). The camera, mirror, and rate sensor were fitted into a spectacle frame. An elastic strap minimized the slippage of the frame relative to the head. The manufacturer's software was used to record and collect the head and eye velocity data (the response).

### Galvanic-induced postural sway assessment procedures

Subjects stood quietly on the force platform for 25 seconds, during which a vestibular sensory illusion was evoked approximately 6 seconds into the trial. 10 trials for each subject were performed and the Center Of Pressure (COP) was recorded. The participants stood without shoes with their head facing forward, eyes open, arms by their sides, heels no more than 10cm apart, and toes angled 20 degrees outward. Participant's height and weight were also noted. Butcher block paper was taped to the force platform and participant's feet were traced on it to ensure that all trials were recorded from the same starting position for pre- and posttraining sessions.

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Table 4.1. Exercise Program and Progression

GPS Exercises	Progression	Duration	Frequency
<b>Gaze</b>			
One target held in hand or wall and horizontal head movements	increased velocity of head movements, smaller sized target, static versus moving background	2.5 min each exercise	4 times per day; total time = 10 mins
Two targets held in hand or wall and horizontal eye movements preceeding head movements to each target	increased velocity of head movements, smaller sized target, static versus moving background	2.5 min each exercise	4 times per day; total time = 10 mins
<b>Posture</b>			
Quiet standing with horizontal head movements	Eyes open versus closed, wider base of support versus narrow BOS	2.5 min each exercise	4 times per day; total time = 10 mins
Quiet standing on compliant surface with horizontal head movements	Eyes open versus closed, wider base of support versus narrow BOS, forward walking with head movements	2.5 min each exercise	4 times per day; total time = 10 mins

Abbreviations: BOS, Base of Support.

Table 4.2. Descriptive statistics<sup>a</sup>

Variables	PwMS (n=19)
Gender (M/F)	3/16
Age	53.4 ± 11.66 (47.80-59.04)
EDSS (min-max)	4.95 ± 1.0 (3.5-6.5)
Diagnosis Duration	16 ± 11.44 (10.49-21.51)
BBT	46.37 ± 7.10 (42.94-49.79)
falls/yr	4.16 ± 3.35 (2.54-5.76)

<sup>a</sup>All values are mean (standard deviation)/95% confidence interval unless otherwise indicated.

Table 4.3. Pre-post median comparisons using separate Wilcoxon signed rank tests

	medians	medians		
Variables	Pre-training	Post-training	Sig (1-tailed)	Effect Size (r)
<i>Body structure and function domain</i>				
<b>aVOR gain<sup>a</sup></b>	<b>0.93</b>	<b>0.92</b>	<b>0.039</b>	<b>0.32</b>
<b>CS/HR<sup>a</sup></b>	<b>0.41</b>	<b>0.61</b>	<b>0.020</b>	<b>0.37</b>
CS Latency (ms)	248.91	197.18	0.058	0.32
GPE (deg)	1.89	1.94	0.056	0.29
<b>ML sway amplitude (mm)<sup>a</sup></b>	<b>20</b>	<b>15</b>	<b>0.018</b>	<b>0.38</b>
Time to restabilization (sec)	8.6	9.1	0.356	0.07
<i>Activity domain</i>				
<b>FGA<sup>a</sup></b>	<b>14</b>	<b>22</b>	<b>0.0005</b>	<b>0.62</b>
<b>FSST (sec)<sup>a</sup></b>	<b>9.64</b>	<b>8.22</b>	<b>0.0005</b>	<b>0.62</b>
<i>Participation domain</i>				
<b>ABC (%)<sup>a</sup></b>	<b>54.38</b>	<b>73.75</b>	<b>0.002</b>	<b>0.52</b>
<b>DHI<sup>a</sup></b>	<b>46</b>	<b>32</b>	<b>0.0015</b>	<b>0.55</b>

<sup>a</sup>  $p < 0.05$  one-tailed significance (bold)

Abbreviations: CS/HR, Compensatory Saccades per Head Rotation.

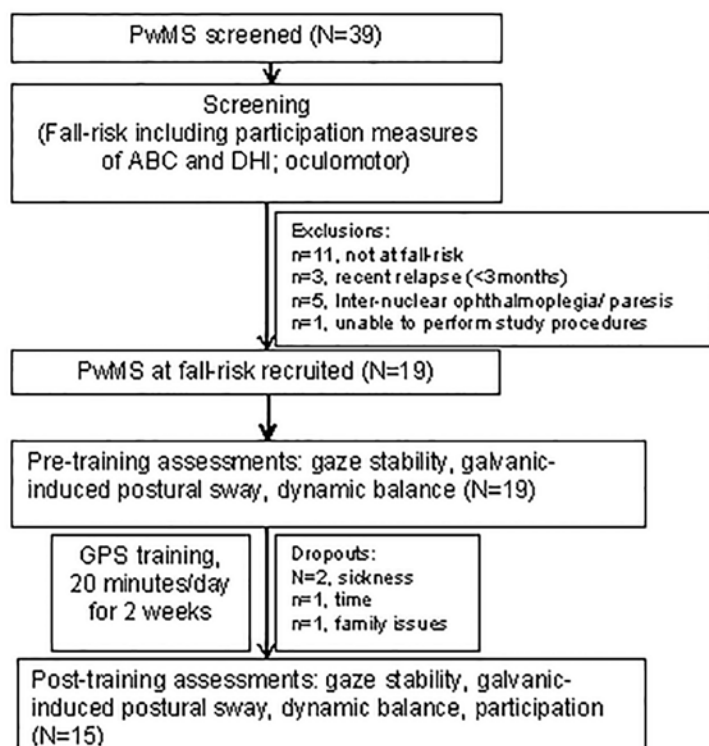


Figure 4.1. Diagram illustrating the flow of participants through the trial.

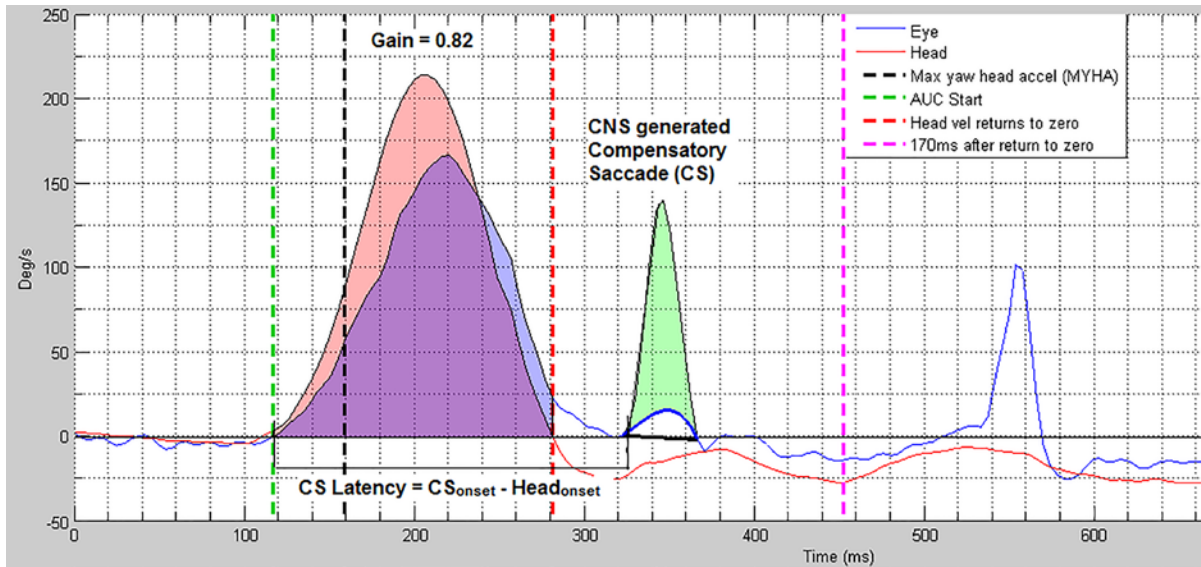


Figure 4.2: Variables of gaze stability. The eye velocity has been inverted for ease of comparison. Subject with MS demonstrating decreased aVOR gain (0.82) and an overt saccade within 170ms of head velocity crossing zero.

Abbreviations: CNS, Central Nervous System; MS, Multiple Sclerosis.

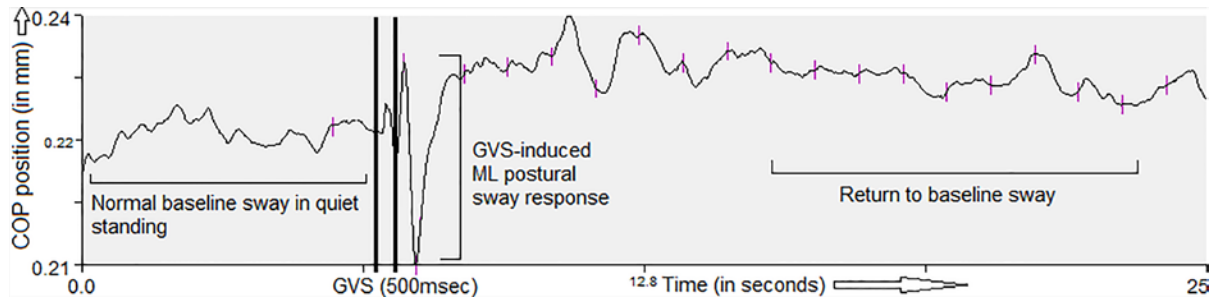


Figure 4.3: Galvanic-induced postural sway response in a subject with MS. The coefficient of variation of COP in the return to baseline sway section is not different from the coefficient of variation of COP in the normal baseline sway section.

Abbreviations: MS, Multiple Sclerosis.

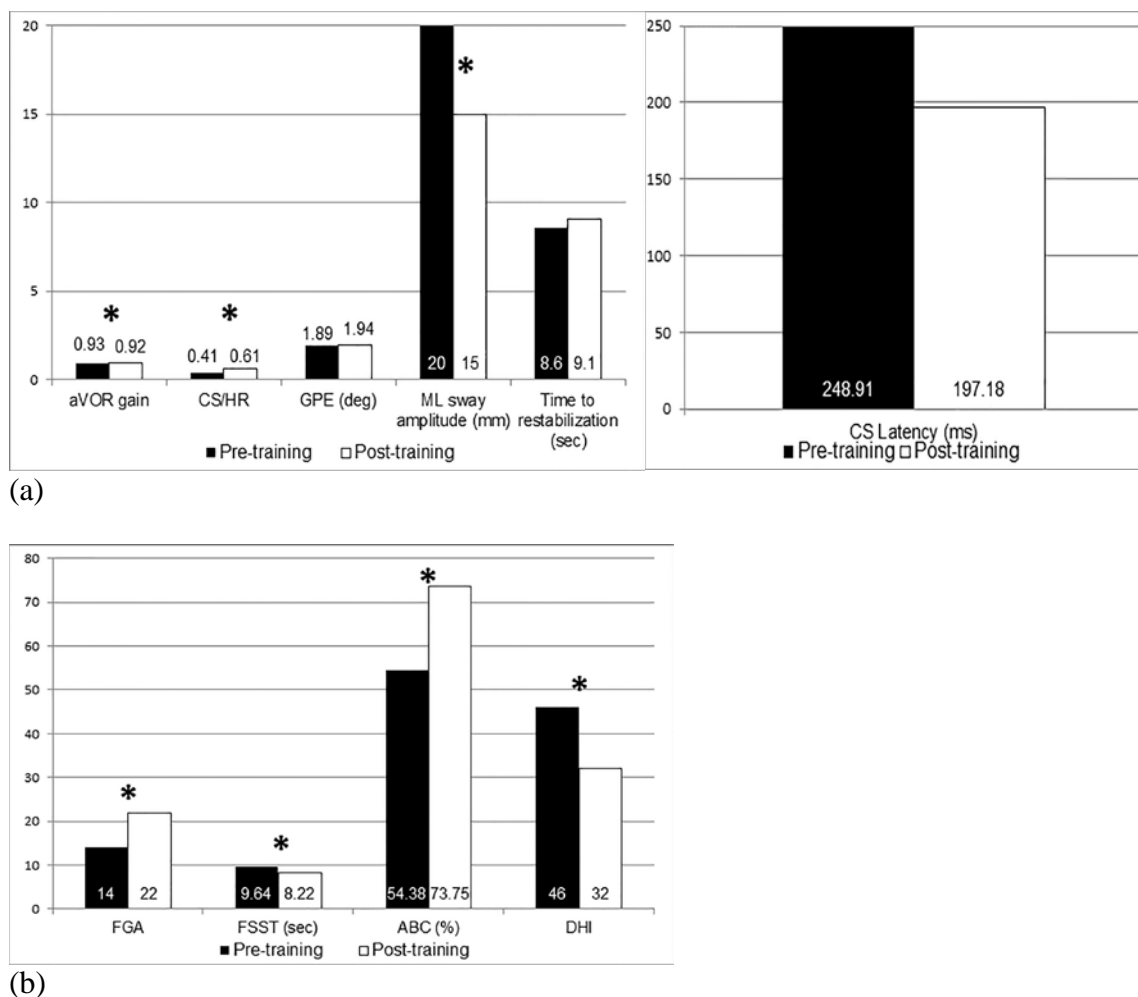


Figure 4.4. Pre- and posttraining median scores.

(a) Pre- and posttraining median scores for measures of body structure and function (gaze stability and galvanic-induced postural sway).

(b) Pre- and posttraining median scores for measures of activity and participation (dynamic balance and self-report).

\*  $p < 0.05$  one-tailed significance.

Abbreviations: CS/HR, Compensatory Saccades per Head Rotation.



## CHAPTER 5

### GENERAL DISCUSSION

Balance and postural impairments are significant complaints in Persons with Multiple Sclerosis (PwMS),<sup>1</sup> and are frequently associated with injurious falls.<sup>2, 3</sup> Accurate sensory perception and central integration of vestibular sensations is essential for optimal gaze, head and body orientation; a deficit in either may subsequently result in imbalance and falls.<sup>4</sup> In MS, the demyelination of afferent or efferent vestibular nuclei pathways that reside within the brainstem and cerebellum may adversely affect the gaze, postural stability, and community participation, thereby necessitating the need to quantify such deficits. In addition, the psychometric properties of physiologic gaze and postural stability assessment measures have not been examined in PwMS. Lastly, despite the frequent inclusions of head and body movements in balance retraining, the efficacy of a Gaze and Postural Stabilization (GPS) intervention on specific gaze and postural stabilization mechanisms as well as on the clinical and self-report measures of activities of daily living have not been well-illustrated in PwMS. This dissertation was therefore undertaken to determine the vestibular-oriented deficits and adaptations in PwMS by employing various outcomes spanning the 3 domains of the World Health Organization's International Classification of Function, Disability, and Health (ICF) model.<sup>5</sup>

Our first study examined the gaze stability, dynamic balance and self-reported

participation deficits in PwMS at fall-risk relative to neurologically healthy age-matched controls. This study identified significant between-group differences in the gaze stability measures (CS/HR, CS latency, Gain CV) such that greater number of compensatory saccades at earlier onset latency and an increased variability of aVOR gain were evident in PwMS as compared to controls. These findings are generally symptomatic of deficient aVOR gain mechanisms. Moreover, PwMS demonstrated impairments in dynamic balance (FGA, FSST) and self-reported participation (DHI, ABC) which highlight the postural and functional difficulties experienced by this group relative to neurologically healthy controls. Another aim of this study was to investigate the relationship between gaze stability and activity and participation measures. Significant relationships between measures of gaze stability (Gain CV, CS latency) and activities (FGA) were determined which suggest that gaze stability defects may be associated with postural instability during walking. Contrary to the hypotheses, this study did not find significant between-group differences in other gaze stability measures (aVOR gain and GPE). However, the insignificant findings can be attributed to high sample variability in accomplishing gaze stabilization during passive head rotations and to the lack of statistical power due to small sample size. Taken together, these findings indicate that gaze stability, dynamic balance, and self-reported participation are affected in PwMS and support the assertion that gaze stability examinations should be included in dynamic balance assessments for persons with MS at identified fall-risk.

The second investigation aimed to examine the psychometric properties of gaze stability, postural sway, and dynamic balance measures by assessing the agreement and response stability between two separate assessments in PwMS and age-matched controls.

We determined that the majority of the gaze stability measures demonstrated moderate test-retest reliability while postural sway as well as dynamic balance evaluations showed good test-retest reliability irrespective of group membership. The variables, aVOR gain, CS latency, ML and AP amplitude, total sway path, FGA, and FSST demonstrated the lowest measurement error and acceptable response stability amongst all the outcome variables. Only the aVOR gain, FGA, and FSST demonstrated low minimal detectable difference, suggesting a low threshold for measurement error. The rest of the outcomes showed high minimal detectable differences suggestive of greater error either in the measurement tool, technique, or from subject variability in performance. The measurement error reflects upon the response stability of a test and is critical to detect true differences in between two sessions beyond that attributable to chance. Information obtained from this study should enhance the interpretation of gaze and postural stability performance changes observed after treatment interventions in PwMS and older adults during routine clinical decision making. Taken together, these results indicate that while aVOR gain, total sway path, FGA, and FSST may be more reliable and sensitive measures to change, a relatively larger change in performance may be needed to detect real change for the remainder of the gaze stability and postural sway measures. Given the novel nature of these findings, these results should serve as a starting point for further research. Future studies should identify the different sources and determine ways to minimize variability in gaze stability and postural sway measures.

The third study intended to determine the effect of a GPS training intervention on gaze stability, galvanic-induced postural sway, dynamic balance, and self-report participation measures in PwMS. Improvements across the entire spectrum of outcome

measures after 2 weeks of home-based training with the exception of aVOR gain were found. With the GPS training, PwMS achieved gaze stability by increasing the recruitment of CS/HR, i.e., substitution strategies. The lack of improvement in aVOR gain may suggest either a diminished ability of PwMS to adapt to high head rotation velocities or the insufficient dosage of GPS training provided to study participants. The improvements seen in galvanic-induced medio-lateral postural sway response, dynamic balance, and self-report outcomes suggest that other strategies such as adaptation and habituation strategies may also be present. Interestingly, the time taken to restabilize after GVS did not change in PwMS. Taken together, these findings suggest that the GPS training benefits the gaze and postural stability as well as increases the self-reported balance confidence and decreases the impact of dizziness during performance of daily activities in PwMS through different strategical mechanisms. Future research should examine the efficacy of GPS training using a randomized clinical trial design, examine skill transfer (passive versus active head rotations), and test for long-term retention of gaze and postural stability improvements in PwMS.

#### Key findings and directions for future research

In this study, significant vestibular-oriented deficits in balance and posture were determined for PwMS across the spectrum of the World Health Organization's ICF model.<sup>5</sup> Deficiencies in gaze stability, postural stability, and subjective participation measures highlight the utility of these assessments in gaze and posture evaluations in PwMS. Moreover, the improvements in gaze stability via substitutive oculomotor mechanisms, in postural stability via postural sway and dynamic balance performance

adaptations, and in subjective participation measures via the physiological adaptations as well as habituation suggest the clinical value of a focused GPS training intervention.

One noteworthy finding of this study was the variability in gaze stability performance in PwMS. Although this variability can be attributed to sample heterogeneity, the population under study, as well as measurement and instrumentation error; the small sample size and varied extent and severity of brainstem and cerebellum demyelination in PwMS may be responsible for the inconsistencies found in this study. Gaze stability is likely achieved by different strategies including adaptation (improvements in vestibular-driven aVOR gain), substitution (use of compensatory saccades with a decreased latency), as well as habituation (diminished subjective response to repeated stimuli).<sup>4</sup> The improvements in substitutive gaze stabilization mechanisms demonstrated by our sample of PwMS after training emphasizes that compensatory oculomotor strategies may contribute to improving gaze during dynamic head and body movements instead of adaptive strategies. Findings from our study therefore warrant the need for larger studies to quantify the vestibular dysfunction and identify the various oculomotor strategies in PwMS to effectively form treatment goals in clinical and research practice. Such studies should consider the correlation of vestibular findings to structural and/or functional neuroimaging to further our understanding of the demyelination effects on brainstem structures.

Additional limitations of this study were the examination of the gaze stability function in only the horizontal yaw plane and the horizontal semicircular canal, the examination of gaze stability only during passive head movements, and examination of COP-based postural function during a static standing task only. Therefore, future studies

should investigate all canal planes via vHIT, include other measures of vestibular structures and function (such as dynamic visual acuity, vestibular evoked potentials, imaging), and examine postural stability during dynamic and multisensory tasks (such as limits of stability, visual or somatosensory sway referencing). Lastly, although we identified compensatory oculomotor strategies in healthy older adults that signify a deficient aVOR gain, due to the study design limitations, we did not examine the effects of GPS intervention on gaze stability in older adults. This finding therefore demands further investigation of gaze stability and treatment approaches in older adults.

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